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ALLERGY ABSTRACTS

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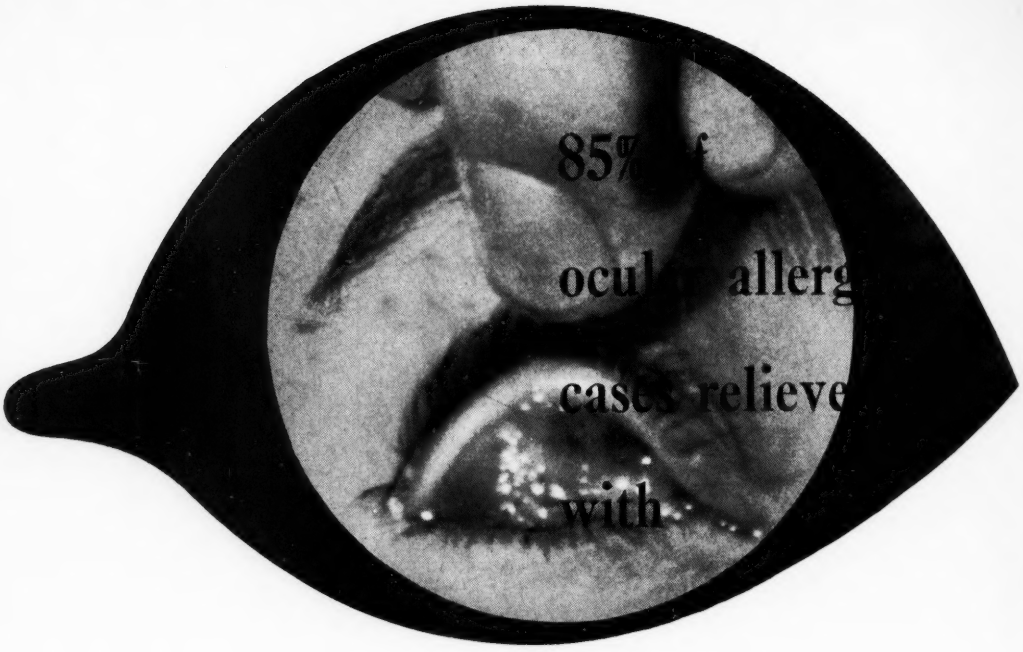

Antistine Ophthalmic Solution

Hurwitz[1] reports symptomatic relief in 85% of 78 patients with ocular allergies treated with Antistine Ophthalmic Solution. This supports his previous conclusions concerning the unusually satisfactory results obtained with Antistine in ocular allergy.[2]

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Issued: Antistine® Ophthalmic Solution containing Antistine (antazoline) hydrochloride, 0.5% in dropper bottles of 15cc.

1. Hurwitz, P.: Illinois M. J. 98:113 (Aug.) 1950.
2. Hurwitz, P.: Am. J. Opth. 31:1409 (Nov.) 1948.
3. St. Clair, C. T. & Bird, B. W.: West Virginia M. J. 46:39 (Feb.) 1950.
4. Friedlaender, A. S. and Friedlaender, S.: Ann. of Allergy 6:23 (Jan.-Feb.) 1948.

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The Journal of Allergy

VOL. 22 MAY, 1951 No. 3

Original Articles

ACTH AND CORTISONE IN ALLERGIC MANIFESTATIONS

THERAPEUTIC RESULTS AND STUDIES ON IMMUNOLOGICAL AND TISSUE REACTIVITY*†

SAMUEL M. FEINBERG, M.D., THURMAN B. DANNENBERG, M.D.,‡ AND SAUL MALKIEL, PH.D., M.D., CHICAGO, ILL.

EARLY claims for the effectiveness of the adrenocorticotrophic hormone and cortisone in asthma and other allergic manifestations[1, 2] have been rather enthusiastic. Improvement of allergic syndromes is notoriously subject to misinterpretation because of cyclic changes and the usual reliance on subjective measurements in allergy. It was decided, therefore, that a study should be undertaken in which the therapeutic effect of these hormones is observed under objective and controlled conditions. In choosing objective methods of study, procedures which may throw light on the mechanisms involved were taken into consideration. In addition to physical findings, such objective steps comprise quantitative titrations of the reaction of the skin to histamine and antigen, the histamine and antigen reaction of the nasal and ocular mucous membrane, the antibody titer and spirometric determinations.

CLINICAL ASPECTS

Scheme of Clinical Therapy.—Asthma cases constituted the greatest part of this group, although several types of dermatologic cases were included. In choosing cases of asthma the following features were considered desirable for our study: an established clinical pattern (seasonal), or consistent symptoms; failure of response to conventional methods of therapy; long-continued observation of the patient by the authors; the presence of recognized allergy and positive skin reactions; associated nasal or ophthalmic symptoms; and a previous hospitalization. We were by no means able to adhere to these ideal qualifications. In choosing patients for this treatment the usual precautionary measures were observed, in order to exclude such conditions as cardiac failure, diabetes, psychoses, hyperadrenalism, and febrile and infectious states.

The patients were hospitalized and preliminary observations were made. In addition to observing the clinical behavior under hospital conditions the

*From the Allergy Research Laboratory, Department of Medicine, Northwestern University Medical School, and Passavant Memorial Hospital, Chicago, Ill.

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‡Present address: Permanente Hospital, Oakland, Calif.

following determinations were done: urinalyses, blood cholesterol and cholesterol esters, absolute eosinophil counts, daily weight recordings, measurements of fluid intake and output, spirometric tests, and skin and mucous membrane titrations with histamine and antigens. In addition, blood was drawn for antibody studies. After early experience the cholesterol determinations and fluid intake and output were found either not significant or unnecessary, and, therefore, were abandoned. We made no attempt to study ketosteroids, because the behavior of the latter had been well established. The procedures outlined were repeated at intervals during therapy. Placebo therapy such as cholesterol, Artisone or normal saline injections was used in certain cases during the initial pretreatment period and sometimes between courses of hormone therapy. The low sodium diet usually was supplemented by a total daily dose of about 2 Gm. of potassium chloride or acetate.

The primary scheme of therapy was to give a brief course of ACTH or cortisone and to observe the duration of effect of such a course. The duration of the therapy varied from 4 to 29 days, but usually averaged 6 to 8 days. In some patients treatment was resumed when a relapse occurred. The injections of ACTH were given 4 times daily, usually in 20 mg. doses. If after 48 hours there was not sufficient response the dose was raised, the highest total daily amounts being 160 mg. For most patients, the total dose for the course was about 400 to 500 mg. although in 3 it was over 1,000 mg. If the response was satisfactory the doses were gradually reduced, beginning about the fourth to the fifth day. The purpose of this was to prevent withdrawal symptoms, rather than to determine the smallest effective dose. The eosinophil response was observed regularly and was sometimes used as a guide to dosage. If the response was considered unsatisfactory cortisone was added while the ACTH was continued or diminished. Several patients were placed on cortisone from the start. The daily dose in such cases was 200 mg. the first 2 or 3 days, reduced subsequently to 100 mg. The total daily dose was divided into 2 injections per day, and later given once daily. Except for very minor measures, other antiallergic therapy was avoided during the hormone administration.

CLINICAL RESULTS

Fifteen asthma patients were observed (Table I). There were 8 males and 7 females, and the ages ranged from 3½ to 70 years, 5 patients being 59 years or older. The duration of the asthma was from 4 months to 54 years, 6 patients having the disease for 16 years or longer, and only one having it less than 2 years. The asthma in most instances was severe and intractable and usually continuous. Four had marked emphysema, 2 of these cases being of such advanced degree that the patients were markedly dyspneic on complete rest and even following the use of bronchodilators. Six had definite evidence of vasomotor rhinitis. Our previous studies failed to demonstrate any positive skin reactions to allergens in 9 of these patients. Positive reactions were present in 6, and, although in some of them multiple sensitivity was present, all of them showed a good skin response to either ragweed, mold, or house dust.

The onset of improvement varied, with a change being noted within 24 to 48 hours in most patients whose subsequent results were satisfactory. In some the relief occurred even more rapidly. Six patients obtained complete relief, all of them on ACTH. Incomplete, yet satisfactory relief was obtained in 4, 2 of these with ACTH, one with cortisone, and one with ACTH followed by cortisone. Associated nasal symptoms also improved, but less rapidly and less markedly than the asthma. In 5 patients the results were slight or questionable. Of these 5, the different circumstances are worthy of note. Two patients (Patients 1 and 9) had a history of asthma of many years but since we have observed them emphysema has been the prominent feature, while wheezing was generally absent and bronchodilators produced little relief. Although somewhat improved with the first course of ACTH and cortisone therapy, Patient 1 failed to respond to a second course later and shortly thereafter died, probably of cardiac failure. Patient 12 claimed to have extreme asthma but we never saw him in other than moderate dyspnea. He was markedly neurotic with frequent hospitalizations. Patient 15 was treated on 2 occasions, the second time while in acute status asthmaticus. This patient has a high degree of mold sensitivity and had been observed by us on a number of occasions, although his desensitization treatment had been carried out in Sioux City, Ia., where he lived. In Sioux City his hospitalizations for status asthmaticus had required 3 week periods. Here, with ACTH therapy he was on his feet in a week and he felt that the attack was shortened. We were not much impressed with his response to ACTH or cortisone. Patient 2, 3½ years of age, had had frequent attacks of asthma since 6 months of age. The child had been hospitalized by the physician-father on a number of occasions, usually with prompt relief followed by a recurrence within a week or so. On ACTH in the hospital the child had a prompt clearing of the asthma, but relapse followed within a week.

Following cessation of treatment relapses occurred in the majority. In 5 the asthma recurred within a week. In 5 recurrence was evident in from 10 to 30 days. In 5 there has been no or only slight recurrence after 14, 28, 90, 100, and 150 days, respectively. Patient 5, a 70-year-old man, had had continuous asthma for 5 years, with no identifiable allergy. He was admitted to the hospital in acute status asthmaticus under oxygen. He made a prompt recovery and has not had any recurrence after 150 days. His respiratory function has increased even beyond the immediate posttreatment period. A long-lasting, severe, seborrheic dermatitis also disappeared.

From the percentage changes in vital capacity and maximum minute volume it is noted that these respiratory function tests reflected fairly well the respiratory relief of the patient, the maximum minute volume being more significant. These readings were made with a pocket-size apparatus consisting of a plastic bag, a two-way valve and a calibrated gauge. In making a determination of maximum minute volume the patient inspired outside air through one valve and expired it through the other valve into the bag. This was done rapidly and forcibly for 30 seconds. The bag was then attached

TABLE I. SUMMARY OF PATIENTS

PATIENT		AGE (YEARS)	SEX	DIAGNOSIS	DURATION (YEARS)	SKIN REACTIONS	TOTAL DRUG (MG.)	
1	J. J.	59	M	Asthma, emphysema	20	0	Cortisone ACTH	2900 600
2	G. R.	3½	F	Asthma	3	0	ACTH	235
3	A. B.	43	F	Asthma	2	0	ACTH	340
4	E. D.	24	F	Asthma, rhinitis	4	0 (Aspirin)	ACTH	510
5	G. M.	70	M	Asthma (acute status asthmaticus), seborrheic dermatitis	5	0	ACTH	460
6	P. G.	57	F	Asthma, rhinitis	15	0	ACTH Cortisone	545 1400
7	J. R.	24	F	Asthma, rhinitis	6	0	ACTH	500
8	B. B.	45	M	Asthma, rhinitis	4 mo. 10 yr.	0 0	ACTH Cortisone	400 1200
9	R. R.	55	M	Asthma, emphysema	9	0	ACTH Cortisone	500 3000
10	S. B.	63	M	Asthma, emphysema	2	Dust (Aspirin)	ACTH	660
11	B. T.	66	M	Asthma, emphysema	54	Dust, ragweed	Cortisone	1150
12	E. S.	26	M	Asthma, rhinitis	19	Dust, mold, ragweed	ACTH	1180
13	G. P.	17	F	Asthma, hay fever	16	Dust, dog, ragweed	ACTH	400
14	M. F.	62	F	Asthma	23	Dust	ACTH	390
15	E. M.	31	M	Asthma, rhinitis	20	Mold	ACTH Cortisone ACTH	510 550 1130
16	B. M.	22	F	Atopic dermatitis, hay fever, and asthma	19	Epidermals ragweed	Cortisone	1200 2500
17	M. H.	62	M	Penicillin reaction	21 days		ACTH ACTH	380 250
18	F. B.	52	M	Eczematoid dermatitis	6		ACTH	280
19	A. S.	76	F	Penicillin reaction?	14 days		ACTH	1010
20	S. F.	55	M	Hay fever	27	Ragweed	ACTH	620
21	F. M.	36	M	Hay fever	?	Ragweed	ACTH	400
22	A. F.	28	M	Hay fever	5	Ragweed	ACTH	520

Skin reaction column: "Aspirin" does not mean a positive skin test, but it signifies clinical sensitivity.

Remission column: + = remission had still not occurred at that time
− = indeterminate period

TREATED WITH ACTH OR CORTISONE

TREATMENT (NO. OF DAYS)	RELIEF	REMISSION (DAYS)	EOSINOPHIL DROP (%)	VITAL CAPACITY (% INC.)	MAXIMUM MINUTE VOLUME (% INC.)	TITRATION CHANGE		
						SKIN	NOSE	EYE
14	Slight	2	49	80	66	H-0		
11				–28		Pk-0		
8	?	7	100					
6	Complete	90+	85	50	44	H-0		
6	Moderate	21	91	33		H-0		
9	Complete	165+	100	20	100			
6	Moderate	28+	90	155	360	H-0	H-1±	H-0
14								
15	Complete	14	98	18	64	H-0	H-0	H-0
10	Complete	14						
	Slight	--						
7	None		70	0	23	H-0	H-0	H-0
28	Slight							
9	Complete	100+	50	20	39	H-0		
						Dust-0		
8	Moderate	30	82	53		H-0		
						Rag-0		
11	Slight	7	84	12	30	Alt-0	Alt-0	Alt-0
						H-0		
8	Complete	10	93	33	108	Rag-0	Rag-0	Rag-0
8	Moderate	8	93	44		H-0		
						Dust-0		
6	Slight	7	57	18	133	Alt-0	Alt-0	Alt-0
7			68					
9								
8	Complete	5	80			H-0	H-0	H-0
28	Complete	–				Rag-0	Rag-0	Rag-0
6	Complete	5	86			H-0		
3	Complete	–						
4	Complete	–	57					
29	Complete	7	99					
9	?	–				Rag-0	Rag-1	Rag-0
7	?	–					Rag-1	Rag-0
7	?	–				Rag-0	Rag-0	Rag-0

Titration column: H = histamine
Rag = ragweed
Alt = alternaria
0 or 1 = changes in reactivity after ACTH. A figure of 1 would indicate that the tissue could tolerate the one concentration higher of the solution after ACTH therapy.

to the special spirometric gauge and the air forced through it. This reading was then multiplied by 2.

The figures on eosinophils listed in Table I indicate the decrease in percentage, comparing the pretreatment count with the average maximal effect. It is difficult to draw any conclusions from these figures, the degree of decrease apparently having very little relation to the degree of therapeutic effect.

The 7 patients treated for syndromes other than asthma were as follows: Case 16, a 22-year-old girl, had a generalized and weeping atopic dermatitis. She had had this eczema since the age of 2, but the severe symptoms were periodic. She was hospitalized for 8 days, received a total of 1,200 mg. of cortisone, with improvement beginning on the third day. In a week she was free of all but some of the chronic indurative changes. Five days following release from the hospital the dermatitis began to recur. At the end of 6 more days the condition was approaching the degree of severity present on admission to the hospital. Cortisone then was given once daily while the patient was ambulatory, the dose varying from 100 to 150 mg. It was a week before improvement was discernible, and at the end of 3 weeks the condition returned to the same improved state as was present when she left the hospital.

Patient 17 had a severe generalized penicillin reaction with formation of large bullae. When seen in the hospital 21 days after the onset of the syndrome, administration of ACTH was followed by a dramatic change in 24 hours, and in 3 or 4 days the lesions had completely cleared. In 10 days there began recurrence of the urticaria. When these lesions became more progressive ACTH was again administered with a rapid resolution and without any subsequent recurrence. Patient 19 was an elderly woman who had a syndrome of marked weakness, urticaria, and angioneurotic edema, fever, high eosinophil count (2,500 to 3,000 per c.mm.), and vague neuritic and muscular pains. This syndrome appeared to follow the classical interval after penicillin administration. The administration of ACTH was followed by a dramatic improvement. After discontinuance of the ACTH there was a recurrence in several days. While the patient was on the second course of ACTH she developed a thrombocytopenic purpura. Among the possible causes responsible for the thrombocytopenia were the ACTH, the quinidine which she was taking for the control of an auricular fibrillation, and the penicillin syndrome. The ACTH and quinidine were discontinued, but a total absence of platelets was noted for more than a week, and then the thrombocytes gradually began to return. It was suspected that polyarteritis might be present but the attending physician was unable to obtain permission for a biopsy.

Patient 18 was a 52-year-old man who had had recurring attacks of severe generalized eczematoid dermatitis over several years. No etiologic factor could be discovered and a brief course of ACTH therapy was accompanied by a prompt remission.

It was planned to treat a special series of hay fever patients during the 1950 ragweed season for the purposes of clinical and immunologic evaluation. However, the abnormally mild season influenced us to keep on postponing

the experiment until it was too late. Three ragweed-sensitive members of the personnel associated with our research organization did subject themselves to a therapeutic and immunologic study. While the mildness of the season made the interpretation difficult, the impression of all 3 participants was that they had no definite abolition of their moderate symptoms as a result of ACTH therapy.

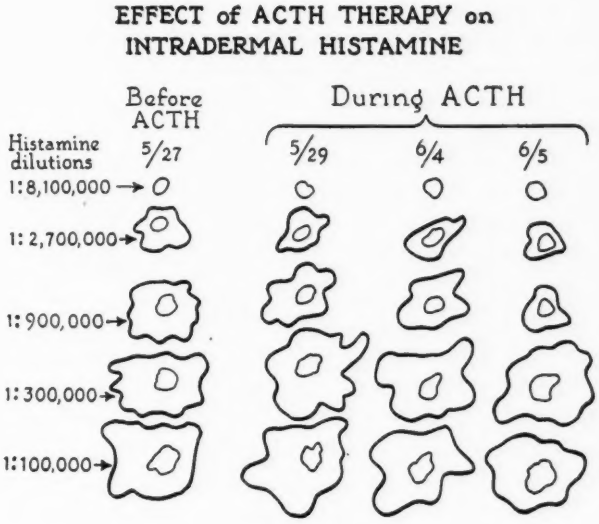

Fig. 1.

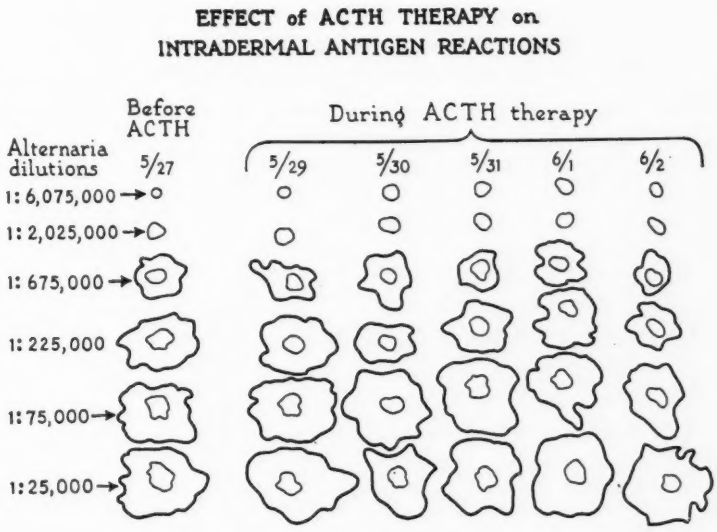

Fig. 2.

Figs. 1 and 2.—Tracings of the wheal and flare of intradermal histamine and alternaria extract in the same patient treated with ACTH. It should be noted that there are no significant changes in the flare with treatment. All subjects were studied is a similar manner with results approximately those shown here.

ANTIGEN-ANTIBODY RESPONSE AND NONSPECIFIC TISSUE REACTIVITY

Skin Tests.—If ACTH or cortisone improves allergic syndromes, the first logical expectation would be to find a modified reactivity of tissues. This does not imply that one must presume that the change is in the antibody titer or in the antigen-antibody reaction. But it would seem reasonable to expect that if an allergic person is more capable of tolerating his specific allergen clinically, no matter what the mechanism involved, he should also react quantitatively less by allergen testing or perhaps by testing with a nonspecific edema-producing substance such as histamine.

The first studies were made on the skin with histamine and specific antigens. After preliminary experiments to find the most effective range, solutions of histamine phosphate were prepared in the following strengths (in terms of histamine base): 1:100,000; 1:300,000; 1:900,000; 1:2,700,000; and 1:8,100,000. These 5 dilutions were injected intradermally in volumes of 0.04 ml. Tracings were made of the wheal and flare reactions, although the flares were found to show a better quantitative relationship. These series of tests were made prior to and during the course of the hormone therapy. Table II shows the results of these reactions. The numbers in the body of the table refer to the highest dilution producing a reaction. Thus a figure of 4 would mean that the 1:2,700,000 dilution was positive, while the 1:8,100,000 was negative. It is a striking fact that the end points were remarkably constant and were not affected by the hormone therapy. Fig. 1 is an illustrative example of the tracings of the flares from intradermal histamine in one of the patients (E. Mc.).

For specific skin tests preparations of house dust,* ragweed pollen, and alternaria were used. The ragweed and house dust extracts were made up in

TABLE II. EFFECT OF ACTH/CORTISONE THERAPY ON SKIN REACTIONS WITH HISTAMINE

DAYS AFTER THERAPY BEGAN	0	1	2	3	4	5	6	7	8	9	10	11	12	13
PATIENTS	HIGHEST DILUTIONS REACTING INTRADERMALLY*													
M. F.	4			4		4	4							
E. O.	3	3	3	3		3								
A. B.	4	4		4										
J. R.	4								4					
J. G.	4								4					
R. R.	4			4					4					
E. Mc.	4	4	4	4	4	4	4	4						
J. J.	4	4	4	4	No ACTH		4	4	4	4	4		4	
J. J. (Cortisone)	4	4	3	3	3	4			4		5	4		5
B. T. (Cortisone)	4		4	4										
B. M. (Cortisone)	4							4						
B. M. (Scratch)	5	5	5					5	5					

*The numbers indicate the highest dilutions of histamine reacting intradermally.

Key to the dilutions:

Intradermal histamine	1. 1:100,00	2. 1:300,000	3. 1:900,000	4. 1:2,700,000	5. 1:8,100,000

Note that ACTH or cortisone produces no consistent effect.

*Endo Products Inc., Richmond Hill, N. Y.

dilutions of multiples of 3, beginning with 1:30,000, that is, 1:30,000, 1:90,000, 1:270,000, and so on. The alternaria extract was begun with a dilution of 1:2,700 and made up in multiples of 3 (see Table III). Tests were performed intradermally as with the histamine, all reactions were traced, and the end points noted. This was repeated several times during the hormone therapy. Table IV shows the end points of these tests. It will be noted that there was no change in the reactions in the majority of instances, regardless of the fact that the patient during that period may have been completely free from symptoms. Fig. 2 shows a typical example of reactions in such a patient (E. Mc.). One patient (G. P.) did show a diminution of reactivity.

In one patient who had no identifiable allergy passive transfer of flaxseed reagin was made. The passively sensitized sites reacted to high dilutions of flaxseed protein, but the end point was the same after cortisone treatment in several new series of sensitized sites.

Shock Organs.—Since ACTH or cortisone have no apparent effect on the nonspecific reactivity of the skin nor on the skin reaction from antigen-antibody combination, the next logical thought would seem to be that these hormones may produce an effect in diseased tissue, the shock organ, without necessarily affecting the usual testing organ, the skin. To test this hypothesis the ideal arrangement, of course, would be to subject the shock organ to exposure with graded doses of an antigen which is known to produce the symptoms in that tissue. This would mean spraying bronchi with an antigen in the case of asthma, placing drops or spraying the nose and instilling drops in the eyes in case of hay fever or nonseasonal allergic rhinitis, and testing the skin in atopic dermatitis. It would mean further that the patient at the time of testing prior to use of the hormones must be free from symptoms, since the production of symptoms is the object of the test. The conditions are by no means easy, since rarely are such patients available for hospitalization or hormone administration. Generally speaking, the patients available to us have been those who were very ill and who were having active symptoms from their shock organs. It can be seen why the kind and extent of tests were perforce limited in the present series.

The procedures were as follows: Solutions of the antigens were made in concentrations designated in Table III. The dilutions were either in multiples of 2 or 3. Histamine dilutions were in multiples of 2. An attempt was made to perform these tests at a time when symptoms in the organ to be tested were relatively quiescent. For the most part the subjects were asthmatics who were hospitalized for their asthma but who also had a history of perennial or seasonal nasal or conjunctival allergic symptoms. In this group it was impossible to make any bronchial test before treatment, since all of them already had severe asthma. We, therefore, confined ourselves to nasal and ophthalmic tests.

A measured amount of a weak solution of the antigen was dropped into the nose. If no symptoms occurred after 10 minutes, the next stronger solution was used. This procedure was repeated until a concentration was reached which gave an unquestioned response consisting of sneezing, nasal stuffiness,

TABLE III. DILUTIONS OF TEST MATERIALS

REFERENCE NUMBERS		1	2	3	4	5	6	7	8	9	10
Histamine	I. D.	100T	300T	900T	2,700T	8,100T					
Histamine	S.	300	600	1,200	2,400	4,800	9,600	19T	38T	76T	153T
Ragweed	I. D.	30T	90T	270T	810T	2,430T	7,290T				
Ragweed	S.	33	100	300	900	2,700	8,100	24,300	72,900	218,700	656,100
Dust	I. D.	30T	90T	270T	810T	2,430T	7,290T				
Dust	S.	40	120	360	1,080	3,240	9,720				
Alternaria	I. D.	2,700	8T	24T	72T	218T	656T	1,968T			
Alternaria	S.	100	300	900	2,700	8,100	24T	72T	247T		
Horse Dander	S.	100	300	900	2,700	8,100	24T	72T	247T		
Flaxseed	I. D.	20	100	1T	10T	100T	1M	10M	100M		

This indicates the concentration of the various materials employed and the reference numbers assigned to them.
T = Thousand
M = Million
I.D. = Intradermal
S = Scratch, ophthalmic or nasal

TABLE IV. EFFECT OF ACTH/CORTISONE THERAPY ON SKIN REACTIONS WITH ANTIGENS

DAYS AFTER THERAPY BEGAN		0	1	2	3	4	5	6	7	8	9	DRUG
PATIENTS	SENSITIVE TO	HIGHEST DILUTIONS REACTING INTRADERMALLY										
S. B.	Dust	5	5	5	5							
E. Mc.	Alternaria	7		7	7	7	7	7		7	7	
M. F.	Dust	3		3			3	3				
B. T.	Ragweed	5		5	5		5		5	5	5	C
B. M.	Ragweed, Scratch	5	5	5	5					5	5	C
	Horse Dander	5	5		5					5		
G. P.	Ragweed	10			5			10		5		
J. J.	Passive Transfer, Flaxseed	8		8		8						
S. F.	Ragweed, Scratch	4			4			4			4	
A. F.	Ragweed, Scratch	5			5		5		5			

This shows the highest skin reacting solution of antigen before and after ACTH or cortisone administration. With the exception of one case (Patient G. P.), no effect is noted.

and rhinorrhea. In testing the conjunctival response, a drop of the solution was placed in the conjunctival sac and successive increases in concentration tested as before. A response consisted of itching, reddening, and swelling of the caruncula, followed by reddening of the conjunctiva. Similar tests were performed with the histamine solutions. The same tests were repeated at intervals after ACTH or cortisone treatment was in progress. Tests were made at least once and usually oftener during treatment and were always made on the same side as the pretreatment titrations. For the nasal and ophthalmic tests the antigens used were ragweed, alternaria, and house dust.

Table V shows the highest dilutions giving reactions in these tests. It will be seen that in the majority of the patients the pretreatment level or reactivity of either the nose or conjunctiva did not change for the several days during the course of hormone therapy. One exception is G. P., a 17-year-old girl who was hospitalized during the ragweed season. She showed a definite reduction of the reactivity of the nose and eyes to ragweed after several days of ACTH treatment. This is the same patient who showed a reduction in the intradermal test to an antigen. Three ragweed-sensitive persons, members of our research organization, who had about 400 to 500 mg. of ACTH during the height of the season, showed no significant changes in titer of reactivity of the ophthalmic and scratch skin test. However, the results in the nasal titrations indicate that there may be some effect from ACTH therapy. In Tables II and IV it will be noted that B. M., a 22-year-old girl hospitalized for generalized atopic dermatitis, showed no change in the scratch skin test to ragweed, horse dander, or histamine after cortisone treatment.

The reaginic antibody titer for those patients in whom there was a demonstrable allergen was compared before and during hormone therapy by the Prausnitz-Küstner passive transfer technique. Multiple sites on the forearm of nonallergic human volunteers were sensitized by the intracutaneous injection of 0.05 ml. of serum serially diluted 1:2. About 48 hours later challenge was performed in the case of ragweed or tree sensitivity by a single subcutaneous injection in the region of the insertion of the deltoid muscle of 0.5 ml. of a 3 per cent extract. For house dust and grass sensitivity each

TABLE V. EFFECT OF ACTH/CORTISONE THERAPY ON OPHTHALMIC AND NASAL REACTIONS WITH HISTAMINE AND ANTIGENS

DAYS AFTER THERAPY BEGAN													
PATIENTS	SENSITIVE TO	0	1	2	3	4	5	6	7	8	9	10	DRUG
E. S.	Alternaria	O 5		O 5									
		N 4		N 4									
B. M.	Ragweed	O 8			O 8					O 8			
		N 7			N 8					N 8			
R. R.	Histamine	O 8				O 8				O 8			
		N 7				N 7				N 7			
J. G.	Histamine	O 8								O 6			
		N 7								N 7			
J. R.	Histamine	O 8								O 8			
		N 7								N 7			
B. T.	House dust	O 4	O 4						O 4				Cortisone
B. T.	Ragweed	O 5				O 5							Cortisone
B. M.	Histamine	O 7			O 7					O 7			Cortisone
E. M.	Alternaria	O 2	O 1		O 2*			O 2					ACTH and Cortisone
G. P.	Ragweed	O 9				O 7		O 4					
		N 11				N 9		N 6					
A. F.	Ragweed	O 5	O 5			O 5		O 5					
		N 5	N 5			N 4		N 4					
F. M.	Ragweed	O 5						O 4	O 5				
		N 4						N 4	N 3				
S. F.	Ragweed	O 5	O 5		O 4	O 5	O 4	O 4	O 4				
		N 5	N 4		N 4	N 5	N 4	N 3	N 2	N 5			

*Discontinue ACTH, start cortisone.

Solutions are same as used on scratch tests.

The numbers indicate the highest dilutions reacting in the eye or nose.

It will be noted that with slight exceptions there is no significant alteration of the reactivity of the ophthalmic or nasal tissue after ACTH or cortisone therapy.

O = Ophthalmic

N = Nasal

individual site was challenged by the intracutaneous injection of 0.02 ml. of extract, 0.1 per cent for house dust and 3 per cent for grass. Reactions to the subcutaneous injections started to appear at about 20 minutes; to the intracutaneous route they were almost instantaneous. In none of the sera tested did there appear to be any difference in the comparative reaginic titer which could be correlated to the hormone therapy.

DISCUSSION

Our clinical results in the treatment of asthma and other allergic manifestations with ACTH and cortisone are on a par with the claims of most workers, but are not as complete or lasting as those claimed by some others.[1-12] This may be due to the types of cases selected by us and to the fact that for the most part no maintenance therapy with the hormones was given. It is almost superfluous to say that those asthma patients whose emphysema is the major factor in their dyspnea will have poor response to these hormones.

Our clinical experience with these agents in allergy, combined with our knowledge of the work of others, shape themselves into a pattern of the uses and limitations of ACTH and cortisone. In acute status asthmaticus these hormones may shorten the course and produce complete relief. However, the

effect of these agents may not be rapid enough in desperate and hazardous situations, and recourse must be had to other measures which may be life-saving, such as epinephrine, intravenous fluids, oxygen, aminophyllin and bronchoscopic aspiration. In chronic asthma, where other methods have been exhausted, it may be permissible to administer maintenance therapy providing small doses are effective and the patient is observed regularly for side reactions. In severe allergic manifestations of limited duration the use of these hormones may be very satisfying, since the remission may be long enough to cover the natural evolution of the disease. Yet the chances of coincidental spontaneous remission make interpretation of favorable hormonal effects hazardous in acute lesions such as many of these. This includes such conditions as reactions to penicillin and sulfonamides. It may also include seasonal allergic manifestations in which the season is not of too long duration. Thus far, unpublished reports of the effects in hay fever have been controversial, and the impression gained is that these hormones may not be very useful for that purpose.

ACTH and cortisone are powerful drugs and must be used only with full understanding of their physiology and the indication for their use. The general release of these hormones to the medical profession is already beginning to result in abuses. We have recently encountered patients who have had asthma of many years' standing who have already been treated with ACTH without any attempt at allergic study and frequently without any serious effort at symptomatic therapy. Many of these subsequently were proved by us to have definite allergies, amenable to allergic management. ACTH or cortisone should not be the first approach to asthma, hay fever, or even acute manifestations such as penicillin reactions. In the majority, competent allergic study and allergic management are much more rational procedures and must precede any thoughts of hormone therapy. In the simpler and acute allergic manifestations palliative therapy is to be tried first.

In addition to the well-known contraindications to and hazards from the use of these hormones, increasing evidence of allergy to ACTH should influence one to undertake the administration of this drug with caution. A number of workers have reported several cases of ACTH allergy[13-16] and we have studied an instance of severe allergy to this hormone.[17] In terms of protein sensitivity a dose of 20 or 25 mg. of ACTH is an enormous quantity of antigen. This warning is especially applicable to our problem since we are concerned with the administration of this agent to people who are primarily allergic.

Our failure to obtain significant results on the immediate skin reaction to antigens and nonspecific whealing agents is in agreement with the findings of most observers,[3, 18-20] although others contend that there is diminution of the whealing skin reaction. One group[7] has claimed that 4 of 5 patients had diminished reactions to intradermal injection of ragweed pollen and dust. However, one would infer from this report that in making the test only one concentration was used and only one test was made during the treatment, the

concentrations of the antigen not being stated. It may be argued that our method of testing is not sensitive enough to disclose any difference in the degree of clinical effect achieved. This argument loses some of its force in view of the fact that striking inhibition of the skin reaction can be disclosed by a single fairly large dose of an antihistamine orally.[21] The failure to find significant changes in the sensitizing antibody does not surprise us. In the first place, changes in the neutralizing antibody (which have not been investigated) could modify the clinical result, and in the second place, there is no particular reason to think that the clinical effectiveness of ACTH or cortisone is likely to depend on a change in the immunologic reaction. However, it would ordinarily be expected that if a patient's tissue reacts less to allergens, in other words, if he is clinically improved, then the effect of the immunologic reaction on the skin test should be reduced and the degree of tissue response should be lessened.

Since the skin responsiveness is not lessened the most logical explanation is that it is not a true measure of the reactivity of the shock organ. The concept of the shock organ naturally revolves around the observation that certain tissues in particular individuals are more susceptible to the effect of an antigen-antibody reaction. It can be presumed that the particular shock tissue is deranged while the skin is not. On the other hand, the apparent failure of significant change in reactivity of the conjunctivae, nasal tissue, and skin after hormone treatment, where these tissues do constitute the shock organ, is more difficult to explain. However, it is possible that here, too, our testing methods were insufficiently sensitive, since with the usual dose of an antihistamine by mouth significant reduction in the reactivity of the shock organ could be shown by the same technique, to an extent appreciably greater than in the skin. It is possible that our patients were not the best subjects for the experiment, that is, we were not dealing as a rule with the major shock organ. This possibility is strengthened by the claims of others[3, 22] who have obtained the blocking of the asthmatic reaction from the inhalation of the specific antigen by prior ACTH treatment.

However, if further and more varied observations under way by our group support our first impression, that the shock organ does not give any changed immediate reaction after hormone treatment, another explanation of this discrepancy is possible. It is not inconceivable that the immediate allergic reaction is unchanged after ACTH therapy and that there is no actual effect on the clinical tolerance to an isolated single exposure, such as the inhalation of antigen in the causation of asthma, the giving of a drug in the production of urticaria, or in the effect of a single feeding of an allergenic food. The repeated and continuous insults from allergic reactions as encountered normally in clinical allergy may, however, result in tissue changes which are considerably different from those in the acute clinical attack or in the experimental testing method. These changes in the tissues which produce chronicity may be susceptible to modification by the hormones and to improvement of the allergic syndrome. It is also possible that even though the degree of an anti-

gen or nonspecific reaction may not be altered after hormone treatment, the duration of the inflammatory reaction may be shortened, thus modifying the pathologic physiology. To throw light on this possibility new types of experimental procedures will have to be tried.

SUMMARY

1. Adrenocorticotrophic hormone and cortisone are of appreciable value in the temporary treatment of certain types and phases of allergic syndromes. They are most helpful in intractable asthma, in acute status asthmaticus, and in severe drug reactions.

2. These hormones have a number of limitations in their usefulness. The length of remissions after a single course of treatment varies from a few days to a few months, the necessity for frequent injections is a handicap, and some types of allergy do not respond.

3. ACTH and cortisone are not substitutes for more basic allergic management.

4. The dangers and hazards from continuous and sometimes from temporary use of these drugs are numerous, and the hormones must not be employed without a full understanding of their many actions.

5. In patients treated with ACTH or cortisone the skin reactions to antigens and histamine remained unchanged.

6. Quantitative studies of the ophthalmic and nasal reactions in those who have nasal and conjunctival allergy show them not to be significantly altered.

7. Sensitizing antibodies have remained unaffected after ACTH or cortisone therapy.

8. It is possible that the simple titration tests do not simulate the conditions of chronic allergy and that tests devised to resemble more closely continuous allergic stimulation might show a more decisive influence of these hormones on allergic reactivity.

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ACTH AND CORTISONE IN ALLERGIC DISEASES*† ‡

Clinical, Serologic (Electrophoretic), and Immunologic Studies

Robert A. Cooke, M.D., William B. Sherman, M.D., Arthur E. O. Menzel, Ph.D., H. Beecher Chapin, M.D., Charles M. Howell, M.D., Roland B. Scott, M.D., Phyllis A. Myers, B.A., and Lillian M. Downing, B.A.

NEW medical discoveries have always commanded prompt and widespread attention. Witness the time and effort spent on anaphylaxis and sensitization, on insulin, liver extract, the antihistamine drugs, and antibiotics. In such instances the area of interest and applicability has been relatively narrow, whereas with the recently developed hormones, ACTH and cortisone, the field at present seems to be almost unlimited.

We now present our clinical and laboratory studies based on the use of ACTH and cortisone in 80 patients representing 96 diseases of allergy (a patient, for example, with both asthma and dermatitis was observed for both diseases and has been counted in both groups).

We shall discuss specifically, and in order, the clinical, serologic, and immunologic aspects of 3 accepted allergic diseases; namely, asthma, dermatitis, and urticaria, and present data based upon those patients observed over periods of weeks to months.

CLINICAL STUDIES

Asthma.—In most of the discussions or papers on this disease asthma seems to be regarded as an entity, although asthma in the infant, asthma in the child and young adult, and asthma developing after 40 years of age, in general, have important differences and implications.

But more important still, when classified on the basis of etiology rather than age of onset, asthma due to inhaled or to ingested allergens is an entirely different problem from that arising on the basis of a bacterial allergy. Therefore, in evaluating hormonal therapy in asthma, attention must be paid not only to such points as the age of the patient, the age of the asthma onset and its duration, but most emphatically to the cause or causes together with such complications as emphysema, pulmonary fibrosis, and cardiac failure.

The great majority of patients with persistent asthma due solely to inhaled allergens, the so-called skin-sensitive type, promptly recover in an allergen-free environment. When the cause is removed the same rapid recovery holds true for the very rare case of asthma due to ingested foods or drugs. Seldom are their attacks prolonged, and withdrawal of the allergen produces relatively prompt relief of symptoms unless infection is also a factor. Such patients sensitive to inhaled and ingested allergens rarely require hormonal therapy because they recover readily on symptomatic treatment together with hospitalization, change of environment or diet, or immunization

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therapy. Two patients (P. Fy. and M. Shds., Table IV) with persistent and severe asthma were hospitalized as candidates for hormone therapy. After the second day of preliminary observation both were free of signs and symptoms. Both were typical examples of sensitization to inhaled allergens in the home. Immunization and home precautions sufficed for such cases.

For our studies with ACTH and cortisone over the past year, we have selected cases from the infective and the combined infective-inhalant groups with persistent severe asthma: patients who did not respond easily to such simple measures as the avoidance of inhaled or ingested allergens. Thirty-one asthmatic patients form the basis for this report.

After a preliminary period of observation for the collection of needed data and to establish a base, patients were started on cortisone or ACTH, as the case may be. The dosage was rarely over 100 mg. per day for cortisone or 80 mg. of ACTH in adults in equally divided doses at 6 hour intervals. With children and infants the doses were reduced to one-half or less of the adult dose. Occasionally a patient was comfortably free of dyspnea by the third day, but in severe cases recovery took from 10 to 14 days. In practically all cases the relief of dyspnea eventually was substantial. As had been the usual experience, this continued as long as the therapy was continued in adequate dosage. On cessation of hormone treatment, asthma returned in a matter of days or at most, a few weeks if, as was often the case, the causative factor was still present.

Latterly, 11 of the group have been on continuation treatment as ambulatory patients for from 2 to 11 months. Four of them, with asthma starting at 50 years of age or above, belonged in the purely infective group, while the rest, with onset between 20 and 35 years of age, had asthma of the mixed type; that is, they had clinical and skin test sensitivity to pollens, molds, or dust in addition to infective asthma usually with chronic bronchitis, hyperplastic pansinusitis, or other foci of infection. The maintenance dose for reasonable comfort varied, but on the average, amounted to 25 to 75 mg. per day given by injection once a day or every other day. More recently, with oral cortisone therapy available, a similar dose seemed to be reasonably, but not quite equally, effective; however, our experience with this was limited to a few cases and for a period of time too short for accurate evaluation.

The beneficial effects on appetite, weight, and general sense of well being were in harmony with the already numerous reports. In no patient was the blood pressure adversely altered; the sedimentation rate if elevated was lowered. With the doses used, there was no evidence of potassium deficiency, marked general edema, acneform eruptions, or sensitivity reaction to the drugs; 2 of our patients became psychotic, but on withdrawal of the medication, recovery ensued in from 2 to 3 weeks.

The blood eosinophil count has shown a decrease with the beginning of hormone treatment, but in many cases has remained considerably higher than normal levels even when satisfactory symptomatic relief was obtained. With the continuation of treatment controlling the allergic symptoms, the eosinophil

count may rise to levels of 1,000 per cu. ml. or higher. For example, patient L. Pzz., while free of asthma on cortisone treatment, had a total eosinophil count of 1,576 on one occasion. In other words, the blood eosinophil count was not a satisfactory index of therapeutic adequacy or clinical results.

The intake of sodium has been restricted in those patients who showed a rapid or excessive gain in weight, but in the case of patients obviously dehydrated by a prolonged illness, a reasonable water retention was considered beneficial. A moderate reduction of sodium and the administration of potassium was considered indicated for patients with whom therapy was continued for a prolonged period after discharge from the hospital. Such continuation therapy has been employed in several cases and will probably be used more frequently when oral cortisone is freely available.

The vital capacity as determined by a simple spirometer generally showed improvement comparable to the symptomatic relief, though rarely with a return to the estimated normal; however, in older patients with fibrosis and emphysema, vital capacity was not increased in proportion to subjective relief. This may be explained as due to the restricted physical exertion in hospitalized patients; the entrance and exit of air is facilitated by the lessened bronchiolar congestion, though there is no change in the elasticity of pulmonary tissues or the fixation of the chest wall. This is illustrated by patient J. Btz. (Table I). He was 72 years old and had had asthma for 15 years. His vital capacity on admission was 800 to 900 c.c., and when he was at his best under hormone therapy, it was never better than 1,200 c.c. which was about 30 per cent of the estimated normal value. He had 7 hospital admissions for cortisone and ACTH treatment between March and December, 1950. At first, after 11 days of hormone treatment, he felt well enough to go home and even to resume business with his vital capacity only one-third of normal. In a week he returned to the hospital in severe status asthmaticus. On this admission he again improved after 10 days of cortisone treatment, but relapsed promptly when the drug was discontinued so that a total of 3 courses over a period of 10 weeks was required before he left the hospital. From this time on, whether in or out of the hospital, he was on continuation therapy with doses of 50 to 100 mg. of ACTH or cortisone per day, but at no time was the chest really free of signs. Early in December, 1950, while on hormone treatment, he died of what seemed to be cardiac failure, although the electrocardiogram the day before death did not show changes indicating potassium deficiency or progressive myocardial disease. No autopsy was permitted.

Dermatitis.—Eleven patients with intrinsic allergic dermatitis (eczema), 6 adults and 5 young children, were selected for our study. What has been said for asthma could be repeated here for dosage and clinical results. In contrast to the intrinsic dermatitis, there were 2 patients (L. Evn. and A. Gpp., Table II) with generalized dermatitis caused by external contact, proved by positive patch test and clinical observation. One (L. Evn.), whose dermatitis was due to Furacin, cleared rapidly with 3 days of hormone therapy and has remained free for months as such patients do in the absence of contact, even

TABLE I. SUMMARY OF PATIENTS WITH INFECTIVE ASTHMA

PATIENT	PRESENT AGE IN YEARS	ONSET AGE IN YEARS	PRIMARY FOCUS	COMPLICATION	ASSOCIATED ALLERGY	PRIMARY THERAPY					MAINTE
						HORMONE USED	DAILY DOSAGE IN MG.	NUMBER OF DAYS OF HORMONE THERAPY	DEGREE OF RELIEF	DURATION OF RELIEF	DAILY DOSAGE IN MG.
C. Wms.	69	68	Bronchi	None	None	Cortisone	100	10	++++	2 weeks	50
E. Dsn.	58	49	Sinus	Emphysema and fibrosis	None	ACTH	100	9	++++	3 days	25
L. Tbx.	74	57	Sinus	Emphysema and fibrosis	Hay fever	ACTH	100	7	+++	10 days	None
T. Dxn.	50	49	Sinus	None	None	ACTH	80	10	++++	3 weeks	None
W. Hkl.	60	57	Sinus	Emphysema and fibrosis	None	Cortisone	100	11	++		25
R. Gdn.	45	42	Sinus	None	None	Cortisone	100	10	+++	6 weeks	None
R. Hki.	49	47	Tonsil and sinus	None	None	Cortisone	100	22	++++		None
Cd. Smt.	64	60	Sinus	None	Vasomotor rhinitis	Cortisone	100	10	++++	2 weeks	25-50
R. Dns.	45	45	Sinus	None	Vasomotor rhinitis	ACTH	80	20	++++	2 days	None
M. Sgr.	49	36	Sinus	None	Vasomotor rhinitis	Cortisone	100	10	++++	6 weeks	None
L. Mse.	40	36	Sinus	None	Vasomotor rhinitis	Cortisone	100	10	++++	1 month	25-75
M. Swz.	49	34	Sinus	None	Vasomotor rhinitis	ACTH	80	12	++++	6 months	None
L. Pzz.	60	54	Sinus	Periarteritis	Eosinophilic granuloma	Cortisone	100	10	+++	6 days	25-50
A. Ktk.	59	53	Sinus	None	Hay fever	Cortisone	100	19	+++		75
R. Isl.	42	39	Sinus	None	Hay fever	Cortisone	100	30	++++	30 days	None
J. Btz.	72	57	Sinus	Emphysema and fibrosis	Vasomotor rhinitis	Cortisone	100	14	+++	10 days	100
H. Cry.	60	59	Sinus	Dermatitis	Hay fever	ACTH	80	12	++++	12 days	None
E. Ndl.	42	34	Bronchi	Emphysema	Vasomotor rhinitis	ACTH	80	6	++++	3 weeks	None
P. Pgn.	51	5	Tonsil	None	Vasomotor rhinitis	ACTH	80	8	++++	3 months	None
J. Slg.	32	29	Sinus	None	None	ACTH	80	10	++	3 days	None
A. Avz.	27	23	Sinus	None	Hay fever	ACTH	80	12	++++	1 month	None
A. Csn.	29	7	Sinus	Dermatitis	Vasomotor rhinitis	ACTH	80	13	++++	2 days	None
N. Nin.	36	13	Bronchi	Emphysema	Hay fever	ACTH	80	20	+	None	80
D. Wlr.	33	10	Sinus	None	None	Cortisone	100	10	++++	2 months	None
H. Vklr.	34	2	Sinus	None	Dermatitis and hay fever	Cortisone	100	15	++++	6 months	None
P. Bll.	11	4	Tonsil	None	Dermatitis and hay fever	Cortisone	100	13	+++	60 days	None
P. Bdn.	15	1	Bronchi	Emphysema	Vasomotor rhinitis and hay fever	Cortisone	80	10	+++	2 months	None
M. Btn.	3½	2½	Tonsil	None	Dermatitis	Cortisone	40	9	+++	2 weeks	None
A. Tnd.	50	43	Sinus	Colitis	Hay fever	Cortisone	75	12	++++	10 days	50
L. Cgm.	38	35	Sinus	Emphysema	Urticaria, vasomotor rhinitis	Cortisone	100	10	+++	2 months	50
Cl. Sth.	66	59	Sinus	None	Vasomotor rhinitis	Cortisone	100	9	++++	10 days	25

*ESR = Erythrocyte sedimentation rate.

without maintenance therapy, but the rapidity of improvement must be credited to the hormone. The other, a florist (A. Gpp.) sensitive to chrysanthemum, recovered so rapidly on hospitalization and local treatment that hormone therapy was not indicated.

The first evidence of benefit was the relief of pruritus usually by the third or fourth day. Gradually then, as scratching ceased, the skin returned to more normal texture. In the infants and young children it became quite normal, save for pigmentation which cleared very slowly, but in the older patients with longer duration of the disease, the chronic tissue changes (licheni-

ASTHMA TREATED WITH ACTH OR CORTISONE

MAINTENANCE THERAPY			CLINICAL DATA BEFORE (A) AND AT END (P) OF HORMONE THERAPY												
DAILY DOSAGE IN MG.	DURATION	ILL EFFECT	WEIGHT		BLOOD PRESSURE		TOTAL EOSINOPHILS		ESR*		RED BLOOD CELL VOLUME		VITAL CAPACITY PER CENT OF ESTIMATED NORMAL		VITAL CAPACITY ESTIMATED NORMAL
			A	P	A	P	A	P	A	P	A	P	A	P	
50	8 months	None	91	104	100/65	135/85	360	331	19	23	48	51	33	59	2740
25	5 months	None	123	127	124/80	138/80	668	212	16		49		57	83	4200
None	None	None	103	115	156/80	196/95	516	216	42	19	44	46	29	55	3160
None	None	None	162	165	136/90	128/88	1227	456	16	25	50	49	28	59	4625
25	None	None	126	127	130/74		366		10		49		40	51	4475
None	None	None	165		120/80		205	75	10	20	49	48	67	99	4825
None	None	None	146	149	130/70	144/90	870		5		52		67	91	4500
25-50	3 months	None	167	161	126/80	110/55	1519		8		53		79		4800
None	None	None	163	165	130/85	140/88	550	86	4	5	48	45	61	83	4100
None	None	None	126	127	140/90	130/90	1040	350	5	11	49	48	52	81	4200
25-75	4 months	None	97	102	130/98	124/90	1587	1256	21	27	49	43	50	90	2750
None	None	None	138	145	134/84	118/72	712	662	9	20	44	39	37	51	3000
25-50	10 months	None	118	125	150/80	124/74	1602	1550	22	48	43	44	22	56	4100
75	2 months	None	163	165	128/84	112/88	1180	1287	11	15	52	49	46	63	4600
None	None	None	200	199	130/86	120/70	635		12		44		20	66	3000
100	9 months	None	106	115	140/85	140/80	192	273	28	36	46	40	26	33	3500
None	None	None	171	178	110/68	112/52	150	156	3		48		70	80	4925
None	None	None	93	97	126/80	134/84	824	414	2	19	37	48	33	66	3000
None	None	None	121	121	128/80		100		23		45		44		3200
None	None	None	120	128	113/74	110/80	400	862	36	17	44	42	73	87	3080
None	None	None	103	109	114/86	110/70	215	340	11	3	45	30	90	85	3800
None	None	None	118	120	130/70	118/78	1900	815	9	15	50	51	60	62	4000
80	50 days	None	110	117	116/68	100/80	714	690	15	23	45	44	35	50	2620
None	None	None	158		110/70		339		12		47		60	84	3700
None	None	None	130	133	98/76	96/64	605	420	23	33	44	44	80	68	3180
None	None	None	58	57			808		40		46		60	84	2500
None	None	None	99		110/70		1140	1237	8	2	50	48	31	69	3235
None	None	None	31	31½			1761		14		49				
50	60 days	None	99	101	110/75	122/80	1534	940	22	16	47	46	106	93	3000
50	5 months	None	110	117	95/80	90/55	717	404	36	29	48	47	75	106	3220
25	6 months	None	100	102	134/82	118/80	1131	719	17	38	48	47	72	83	2880

fication) remained and no patient was under continuation therapy long enough to observe resolution of what was regarded as permanent skin induration.

Here, too, as in asthma, cessation of therapy was followed by a rapid return of symptoms in all 11 cases of intrinsic origin.

Urticaria.—Another group consisted of 5 cases of chronic urticaria of many months' duration. ACTH or cortisone brought relief in 3 to 5 days with a general disappearance of wheals and pruritus. Again, as in asthma and dermatitis, there was little lasting effect unless a cause had been discovered and removed.

TABLE II. SUMMARY OF CASES WITH ALLERGIC

PATIENTS	PRESENT AGE (YEARS)	ONSET AGE (YEARS)	AREA INVOLVED	ASSOCIATED ALLERGY	PRIMARY THERAPY				
					HORMONE USED	DAILY DOSAGE IN MG.	NUMBER OF DAYS OF HORMONE THERAPY	DEGREE OF RELIEF	DURATION OF RELIEF
Adults									*Intrinsic Allergic*
A. Lnr.	49	48	General	Vasomotor rhinitis	Cortisone	100	40	+++	3 days
M. Olt.	48	27	General	Vasomotor rhinitis and asthma	ACTH	80	90	++	90 days
H. Vklr.	43	2 months	General	Vasomotor rhinitis and asthma	Cortisone	100	15	+++	3 months
A. Csn.	29	7	General	Vasomotor rhinitis and asthma	ACTH	80	13	+++	2 days
J. Dgl.	29	2	Face and extremities	Hay fever, asthma	ACTH	80	20	++++	21 days
J. Mtz.	21	6 months	General	Hay fever, asthma	ACTH	80	11	++++	100 days
Infants									
E. Gld.	20 months	7 months	General	None	Cortisone	60	16	+++	10 days
R. Rmm.	2½	6 weeks	General	None	ACTH	40	9	+++	2 months
N. Cno.	2	4 months	General	Vasomotor rhinitis	ACTH	40	7	++++	50 days
V. Stn.	2	2 months	General	None	ACTH	40	47	+	5 days
J. Rdn.	7 months	2 months	General	None	ACTH	40	12	+	7 days
Adults									*Extrinsic Allergic*
L. Evn.	43	43	General (Furacin)	None	ACTH	80	5	++++	3 months +
A. Gpp.	50	50	General (chrysanthemum)	None	None				

*Erythrocyte sedimentation rate.

SUMMARY

As a result of these experiences with various allergies over the last year, we must ask ourselves just what place these new agents should properly have in our practical work as physicians, leaving out of consideration their use in the scientific approach to the basic problems of allergy.

It is our present conviction that we must continue to study patients for the cause of their symptoms just as in prehormone days; in other words, an etiologic diagnosis is just as important now as it ever was, for it constitutes the only sound basis for a long-term effective management program and a prospect of any lasting benefit.

These new hormone drugs have afforded the best means of attaining symptomatic relief yet available, but there is no evidence that they influence the further course of the disease. They are useful to provide physical rest, and to promote improved nutrition and hydration which are badly needed by many of these chronically ill patients. They are also excellent for preoperative preparation of the chronically ill asthmatic patient. In several instances, operations, such as tonsillectomies, have been performed while the hormone treatment was continued and none of these patients have shown excessive operative or postoperative bleeding. Despite suggestions to the contrary, the drugs as employed in this series seem to hasten rather than retard postoperative convalescence. A word of caution must be given as to their wholesale and indis-

DERMATITIS TREATED WITH ACTH AND CORTISONE

MAINTENANCE THERAPY			CLINICAL DATA BEFORE (A) AND AT END (P) OF HORMONE THERAPY									
			WEIGHT		BLOOD PRESSURE		TOTAL EOSINOPHILS		ESR*		RED BLOOD CELL VOLUME	
DAILY DOSAGE IN MG.	DURATION	ILL EFFECT	A	P	A	P	A	P	A	P	A	P
Dermatitis (Eczema)												
50-75	30 days	None	185	177	120/80	128/88	185	108	38	39	38	38
None	0	Psychosis	105	120	160/84	138/100	234	169	40	17	45	47
None	0	None	130	133	99/76	96/64	605	420	23	33	44	44
None	0	None	118	120	130/70	118/78	1900	815	9	15	50	51
None	0	None	199	197	118/62	118/76	994	163	8	9	48	46
None	0	None	130	133	116/58	122/74	465	562	9	39	34	42
None	0	None	24	26			375	38	32	5	35	41
None	0	None	30	32			872	75	12		44	
None	0	None	23	22¾			975		3	5	37	36
None	0	None	26	28			985	1325	11	1	35	37
None	0	None	20	20			225	56	1	1	30	40
Dermatitis (Contact)												
None	0	None			150/95		872		9		51	

criminate use. These drugs mask symptoms without curing the disease. They tend to lower the temperature and leucocyte count where such findings could be an index to serious trouble such as bacteremia or peritonitis. They should not be used unless the patients are under frequent observation.

SEROLOGIC STUDIES

Various chemical and electrophoretic studies on sera of patients have been made at intervals before, during, and after hormone therapy in the doses previously outlined over periods of time ranging from 2 weeks to 11 months.

Methods, Technique and Introductory Remarks.—The sera were analyzed for their total protein content by a colorimetric biuret method based upon Gornall, Bardavill and David's procedure,[1] utilizing refinements in the standardization of the biuret reagent elaborated by us.[2] All analyses were performed in duplicate and the results averaged. The total protein content of these sera (whether analyzed before or after commencement of hormone treatment) was found with rare exceptions to be between 6 and 8 Gm. per 100 ml., a range generally accepted as normal. Chemical gamma globulin determinations based upon the procedures of Jager and Nickerson,[3] and that of Wolfson, Cohn, Calvary and Ichiba,[4] gave mutually consistent results, but failed in many instances to agree with the gamma globulin values obtained by electrophoresis. We therefore concluded that the gamma globulin values obtained by these 2 chemical

TABLE III. ANALYTICAL DATA ON SERA FROM CHRONIC INFECTIVE ASTHMA PATIENTS AGED 40 YEARS OR OLDER*

PATIENT	PRESENT AGE (YEARS)	ASTHMA DURATION (YEARS)	ASSOCIATED SKIN TEST SENSITIVITY	PRIMARY INFECTIVE FOCUS	TOTAL PROTEIN BY BIURET (GM./100 ML.) (7.23†)	ELECTROPHORETIC DETERMINATIONS					
						PROTEIN DISTRIBUTION IN PER CENT					ALBUMIN GLOBULIN RATIO (1.27†)
						ALBUMIN (56.0†)	ALPHA$_1$ GLOBULIN (7.2†)	ALPHA$_2$ GLOBULIN (8.8†)	BETA GLOBULIN (13.1†)	GAMMA GLOBULIN (14.7†)	
J. Btz.	72	15	Dust	Sinus	7.5	47.3	13.9	14.3	9.6	14.9	0.90
H. Cry.	60	1½	Dust, pollen	Sinus	6.8	39.3	10.5	27.7‡		22.5	0.65
R. Dns.	45	½	Dust	Sinus	7.6	49.5	7.4	14.6	14.8	13.8	0.98
E. Dsn.	58	10	None	Sinus	8.0	51.3	11.1	9.6	16.1	11.9	1.05
T. Dxn.	50	½	None	Sinus	7.1	43.2	13.1	16.4	12.9	14.4	0.76
R. Gwn.	45	2½	None	Sinus	8.0	52.5	7.7	12.4	6.9	20.5	1.11
A. Kik.	59	6	None	Sinus	7.1	44.3	8.3	16.7	14.1	16.6	0.80
L. Mse.	40	4	Alternaria, dander	Sinus	8.5	45.9	13.6	15.5	10.0	15.0	0.84
L. Pzz.	60	7	None	Sinus	6.0	38.6	10.5	19.6	12.5	19.0	0.63
S. Rtl.	46	40	None	Tonsils	6.5	45.7	9.6	13.5	14.0	17.3	0.84
M. Swr.	49	13	Dust	Sinus	7.3	50.2	10.8	17.0	10.8	11.2	1.01
Cl. Sth.	66	7	Dust	Sinus	7.3	53.9	10.6	9.8	14.4	11.3	1.17
A. Tnd.	50	7	Alternaria, pollens	Sinus	7.5	47.6	13.6	9.4	11.1	18.3	0.91
C. Wms.	69	1	None	Bronchi	6.8	38.4	10.4	23.5	10.5	17.2	0.62

*None of these patients had hormone therapy prior to these analyses.
†Normal values: see Reference 12.
‡Alpha$_2$ and beta globulins did not separate.

methods did not reflect uniformly the gamma globulin values as obtained electrophoretically in these sera. The usefulness of the turbidimetric method of Kunkel[5] was not explored in our studies. Prior to electrophoresis 5 ml. or 7.5 ml. samples of the sera were diluted with Longsworth[6] barbiturate buffer (pH 8.6, ionic strength 0.1), usually in the proportion 1:2 or 1:3, and dialyzed in the cold by stationary dialysis against 800 ml. of the same buffer, usually for 2 days. Electrophoresis was carried out at 15 Ma., when the voltage gradient was at about 6 volts per centimeter.

Electrophoresis was performed in an Aminco-Stern apparatus, the construction of which is based upon Tiselius' moving boundary method[7] and whose optical system permits observation and photographing of the patterns with aid of a variation of the Philpot-Swensson cylindrical lens and inclined slit system.[8, 9, 10] Most of the analyses and all of the separations were performed in standard analytical cells*; the rest of the analyses were carried out in a "clinical cell."† Tracings of the enlarged photographs of the patterns were made and the percentage distribution of the individual fractions calculated by the method of Tiselius and Kabat.[11] The areas as constructed according to this procedure under the individual protein peaks were measured in planimeter units and the relative concentrations were calculated and expressed in per cent of the total gradient area in the usual manner. None of the data given here was based upon the evaluation of a single pattern; each represents the average from the evaluation of several patterns (usually 4 or more) photographed in the course of the experiment. This procedure allows a calculation of deviations of the values of the individual pattern from the averaged values, and hence it affords, to some degree, a measure of the attained precision.‡ For the present purpose it suffices to state that the data presented are comparable with each other and that their estimated errors in precision approximate ± 2 per cent for albumin, ± 1 per cent each for alpha$_1$, alpha$_2$, beta globulin, and ± 1.5 per cent for gamma globulin. Evaluations of patterns obtained from 5 normal adult sera were found in good agreement with data published about normal sera by Reiner, Fenichel, and Stern,[12] and Seibert, Seibert, Atno, and Campbell.[13] In our tables we used the data of Reiner, Fenichel and Stern (corrected for some obvious clerical errors) as a standard of comparison inasmuch as any elevation of gamma globulin in pathologic sera over Stern's mean value of 14.7 per cent (entire series of 80 sera) would be more significant in interpretation than a comparison with somewhat lower values of other investigators.[14, 15, 16]

The patterns obtained from sera of young children cannot be compared with normal values obtained from adults, for Lubschez[17] reported electrophoretic data on normal children's plasmas and sera indicating a distinctly different distribution of the individual protein constituents. We converted Lubschez's data on 9 electrophoretic analyses of plasmas and sera from individuals in the age group of 2 to 4 years to serum basis and used the calculated averages as a standard of comparison.

*American Instrument Co. Bulletin No. 2175.

†Kindly put to our disposal by Dr. Kurt G. Stern, Brooklyn Polytechnical Institute, and Miss Miriam Reiner, Mt. Sinai Hospital, New York.

‡Presentation of details of this procedure and discussion of general issues involved are reserved for a separate publication.

TABLE IV. ANALYTICAL DATA ON SERA FROM CHRONIC ASTHMA PATIENTS AGED 11 TO 40 YEARS*

PATIENT†	PRESENT AGE (YEARS)	ASTHMA DURATION (YEARS)	CAUSES OF ASTHMA		TOTAL PROTEIN BY BIURET (GM./100 ML.) (7.23‡)	ELECTROPHORETIC DETERMINATIONS					
						PROTEIN DISTRIBUTION IN PER CENT					ALBUMIN GLOBULIN RATIO (1.27‡)
			EXTRINSIC	INFECTIVE		ALBUMIN (56.0‡)	$ALPHA_1$ GLOBULIN (7.2‡)	$ALPHA_2$ GLOBULIN (8.8‡)	BETA GLOBULIN (13.1‡)	GAMMA GLOBULIN (14.7‡)	
1. P. Bdn.	15	13	Dander, dust	Bronchi	7.8	54.6	11.6	11.2	10.2	12.4	1.21
2. P. Bll.	11	7	Dust, mold, pollen	Bronchi	7.7	41.0	10.4	17.7	15.5	15.5	0.69
3. A. Csn.§	29	21	Dust, dander, pollen	Sinus	7.8	53.1	7.5	11.5	11.8	16.1	1.13
4. N. Min.	36	23	Dust, pollen	Bronchi	9.0	48.7	7.9	10.2	12.4	20.8	0.95
5. J. Sgr.	32	4	None	Sinus	7.4	46.9	13.3	10.4	14.0	15.5	0.88
6. P. Fy.	29	11	Dust, dander	None	8.5	57.4	6.4	13.5	13.3	9.5	1.35
7. M. Shd.	36	25	Dust, dander, pollen	None	7.9	56.7	4.2	9.7	13.1	16.3	1.31

*None of these patients had hormone therapy prior to these analyses.

†In Patients 1 through 5 infection was the important cause of chronic asthma; extrinsic causes were secondary. In Patients 6 and 7, extrinsic allergies alone caused chronic asthma. They cleared completely after 2 days of hospitalization.

‡Normal values: see Reference 12.

§This patient was also suffering from dermatitis.

TABLE V. ANALYTICAL DATA ON SERA FROM INFECTIVE AND PERSISTENTLY ASTHMATIC CHILDREN*

PATIENT	PRESENT AGE (YEARS)	ASTHMA DURATION (YEARS)	ASSOCIATED SKIN TEST SENSITIVITY	PRIMARY INFECTIVE FOCUS	TOTAL PROTEIN BY BIURET (GM./100 ML.)	ELECTROPHORETIC DETERMINATIONS					
						PROTEIN DISTRIBUTION IN PER CENT					ALBUMIN GLOBULIN RATIO (1.78†)
						ALBUMIN (64.0†)	$ALPHA_1$ GLOBULIN (4.7†)	$ALPHA_2$ GLOBULIN (9.3†)	BETA GLOBULIN (14.6†)	GAMMA GLOBULIN (7.4†)	
M. Brn.	4	1	None	Tonsils, adenoids	7.0	57.9	8.2	13.1	12.7	8.2	1.37
C. Spk.	2	1	Dust	Tonsils, adenoids	6.3	57.6	8.0	14.5	11.1	8.9	1.36
D. Tpn.	3	2	Dust	Tonsils, adenoids	6.4	57.9	7.5	16.5	12.4	5.7	1.37

*None of these patients had hormone therapy prior to these analyses.

†Normal values: see Reference 17.

Studies on Sera of Patients With Allergic Disease.—These analyses were made on sera from patients with various allergic diseases grouped as to age or cause established by careful clinical examination. The analytical data are presented in Tables III, IV, V, VI, and VII. For purpose of comparison analyses were performed on the sera of 2 patients with bronchiectasis and 2 with osteomyelitis, all without asthma or allergic manifestations. These latter analyses are included in Table VIII.

Asthma: Concerning the serum patterns as obtained from 19 adult patients (Tables III and IV) with chronic intrinsic asthma, it may be said that the albumin-globulin ratio of 4 sera had essentially normal values while in the remaining 15 sera hyperglobulinemia was evidenced by more or less lowered albumin-globulin ratios. Gamma globulin was raised distinctly above normal values in 4 instances, and slightly elevated in several others, while elevation of alpha globulin was distinct in 8 and indicated in several other sera; the beta globulin values were usually within normal range, 6 patterns exhibiting somewhat low values. In one instance $alpha_2$ and beta globulins failed to separate during electrophoresis.

The sera of 2 adult patients (Table IV) whose chronic asthma was due entirely to extrinsic causes showed normal albumin contents and albumin-globulin ratios. One of these (P. Fy.) had evidence of sinus infection, which was apparently not yet a factor in asthma since the attack cleared promptly after 2 days of hospitalization. The serum showed minor evidence of change in an elevated $alpha_2$ and lowered gamma globulin.

All serum patterns of the 3 asthmatic children (Table V) showed lowered albumin and distinctly elevated alpha globulins; the gamma globulin values of these sera were probably within the normal limits for this age group, with the only possible exception of D. Tpn. Gamma globulin deficiency due to a congenital defect in protein formation as reported by Schick and Greenbaum[18] was ruled out in all these instances.

Dermatitis: The patterns from the 5 adult patients suffering from chronic intrinsic dermatitis (Table VI) showed albumin levels in the normal range or slightly depressed; elevation of the alpha globulins, if any, was only moderate, with the possible exception of M. Olt. The beta globulin values appeared to be within normal range, while the gamma globulin values were either somewhat elevated or at the upper limits of the normal range. For comparison the sera of 2 patients with extrinsic (contact) dermatitis (Table VI) showed essentially normal electrophoretic patterns. On the other hand, the gamma globulin values of all 4 children suffering from allergic dermatitis (infantile eczema) in Table VII were significantly elevated. In these sera, elevated alpha globulin values were manifest (in one of the sera, $alpha_2$ failed to separate from beta globulin), and the albumin values were distinctly decreased and the beta-globulin levels normal. Accordingly, the albumin-globulin ratios were noticeably lowered in these sera.

Comparative patterns of sera from patients with chronic suppurative lesions are shown in Table VIII. Two bronchiectasis patients (without asthma

TABLE VI. ANALYTICAL DATA ON SERA FROM INTRINSIC DERMATITIS PATIENTS AGED 21 TO 50 YEARS*

PATIENT	PRESENT AGE (YEARS)	DURATION (YEARS)	ASSOCIATED ALLERGIES WITH WHEAL TYPE REACTION		TOTAL PROTEIN BY BIURET (GM./100 ML.)	ELECTROPHORETIC DETERMINATIONS: PROTEIN DISTRIBUTION IN PER CENT					ALBUMIN GLOBULIN RATIO (1.27†)
						ALBUMIN (56.0†)	ALPHA$_1$ GLOBULIN (7.2†)	ALPHA$_2$ GLOBULIN (8.8†)	BETA GLOBULIN (13.1†)	GAMMA GLOBULIN (14.7†)	
A. Csn.	29	21	Asthma	Dust, pollen	7.8	53.1	7.5	11.5	11.8	16.1	1.13
J. Dgl.	29	26	Hay fever	Dust, pollen	8.4	55.3	5.4	6.7	12.7	20.0	1.24
A. Lnr.	49	2	None	None	7.2	47.0	8.2	9.8	16.5	18.5	0.89
J. Mtz.	21	20	Hay fever	Dust, pollen	7.6	56.1	5.3	10.6	10.6	17.4	1.28
M. Olt.	48	20	Hay fever	Mold, pollen, Dander	8.9	49.0	11.0	13.4	10.7	16.1	0.96
				Extrinsic Dermatitis for Comparison							
A. Gpp.‡	50	25	None	None	6.4	54.5	7.2	11.6	12.2	14.6	1.20
L. Evn.§	43	1½ months	None	None	1.8	54.0	6.7	10.6	13.9	14.9	1.17

*None of these patients had hormone therapy prior to these analyses.
†Normal values: see Reference 12.
‡Patient, a florist, with reaction to chrysanthemum and positive patch test.
§Patient sensitized by Furacin with positive patch test.

TABLE VII. ANALYTICAL DATA ON SERA FROM CHILDREN SUFFERING FROM INTRINSIC DERMATITIS (INFANTILE ECZEMA)*

PATIENT	PRESENT AGE (MONTHS)	DERMATITIS DURATION (MONTHS)	ASSOCIATED ALLERGIES WITH WHEAL TYPE REACTIONS	TOTAL PROTEIN BY BIURET (GM./100 ML.)	ELECTROPHORETIC DETERMINATIONS: PROTEIN DISTRIBUTION IN PER CENT					ALBUMIN GLOBULIN RATIO (1.78†)
					ALBUMIN (64.0†)	ALPHA$_1$ GLOBULIN (4.7†)	ALPHA$_2$ GLOBULIN (9.3†)	BETA GLOBULIN (14.6†)	GAMMA GLOBULIN (7.4†)	
N. Csn.	20	16	Dust, dander	7.2	46.5	9.6	17.5	12.0	14.4	0.87
E. Gld.	20	12	Dust	7.0	40.9	9.6	16.2	15.0	18.4	0.69
J. Rdn.	9	7½	Egg, fish	6.5	49.4	5.7	15.5	11.7	17.7	0.98
V. Stp.	24	21	Dust, dander	6.5	50.7	7.1	28.6‡		13.6	1.03

*None of these patients had hormone therapy prior to these analyses.
†Normal values: see Reference 17.
‡Alpha$_2$ and beta globulins did not separate.

or known allergy) exhibited markedly lowered albumin levels. In one case (S. Lwn.) the corresponding increase in globulin was fairly evenly distributed over all 4 globulin fractions, and in the other (P. Rbg.), the elevation of gamma globulin was especially pronounced. The pattern of one of the osteomyelitis patients (P. Fdz., also nonallergic and nonasthmatic) showed lowered albumin, normal gamma globulin, and increased beta and alpha globulins. The pattern of the second patient was characterized by greatly reduced albumin and greatly increased gamma globulin.

All electrophoretic patterns from this variety of pathologic sera included in Tables III, IV, V, VI, VII, and VIII, exhibited the normal sequence of protein constituents as encountered in normal human sera, except in 2 instances, where adjacent peaks failed to separate from each other. Unusual peaks as in the pattern of a patient with cirrhosis of the liver, reported by Stern and Reiner,[19] were not encountered in any one of our patterns; however, occasionally slight additional peaks in the beta or alpha region were observed. Although 7 of our patients' sera showed essentially normal proportions of the individual protein fractions, the majority showed reduced albumin and accordingly elevated globulin levels.

TABLE VIII. COMPARATIVE ELECTROPHORETIC ANALYSES ON SERA IN CASES OF INFECTIVE ASTHMA, BRONCHIECTASIS, CHRONIC OSTEOMYELITIS, AND LUPUS ERYTHEMATOSUS

		PROTEIN DISTRIBUTION IN PER CENT					ALBUMIN-GLOBULIN RATIO (1.27†)
PATIENT	DIAGNOSIS	ALBUMIN (56.0†)	$ALPHA_1$ GLOBULIN (7.2†)	$ALPHA_2$ GLOBULIN (8.8†)	BETA GLOBULIN (13.1†)	GAMMA GLOBULIN (14.7†)	
R. Dns.	Asthma	49.5	7.4	14.6	14.8	13.8	0.98
P. Fdz.	Osteomyelitis	45.3	8.5	13.1	19.2	13.8	0.83
S. Lwn.	Bronchiectasis	42.1	8.7	13.3	17.7	18.2	0.73
L. Pzz.	Asthma	38.6	10.5	19.6	12.5	19.0	0.63
P. Rbg.	Bronchiectasis	36.3	11.1	11.1	15.7	25.9	0.57
F. Bll.	Osteomyelitis	32.8	9.6	11.6	11.2	34.9	0.49
Reiner's cases*	Lupus erythematosus	33.4	7.3	15.4	12.8	31.1	0.5

*From Miriam Reiner: See Reference 20. Average values of 20 cases of lupus erythematosus.

†Normal values: see Reference 12.

The 2 sera from patients (P. Fy. and M. Shd.) with purely extrinsic asthma included in the series showed essentially normal electrophoretic patterns, suggesting that allergic disease (in the absence of infection) does not, per se, cause abnormalities recognizable by the electrophoretic method. The 2 patients with contact dermatitis (L. Evn. and A. Gpp.), likewise showed normal patterns. Two patients (P. Bdn. and A. Csn.) with long-standing extrinsic asthma had only recently been complicated by superimposed infection, which at the time of examination was an essential cause of asthma. These 2 patients also showed near-normal electrophoretic patterns. The findings in these few cases, if confirmed, suggest that the electrophoretic pattern of the serum might be an aid in the etiologic diagnosis of chronic asthma, where the evaluation of extrinsic and infective causes is not clear on clinical grounds.

Our electrophoretic data on sera from adult patients with chronic infective asthma re-examined from this point of view appear under an entirely new aspect in that the general features of the majority of this type of sera not only resemble the general features of sera from chronic infective cases without allergic manifestations, as included in our studies, but also, to a striking extent, the features of lupus erythematosus sera, as reported by Reiner.[20] It would appear that the latter features represent the final stage in a progressive deterioration of serum protein distribution, while the features of such sera of chronic infective cases, as reported by us, represent merely various intermediate stages in the course of progressive deterioration. The point is

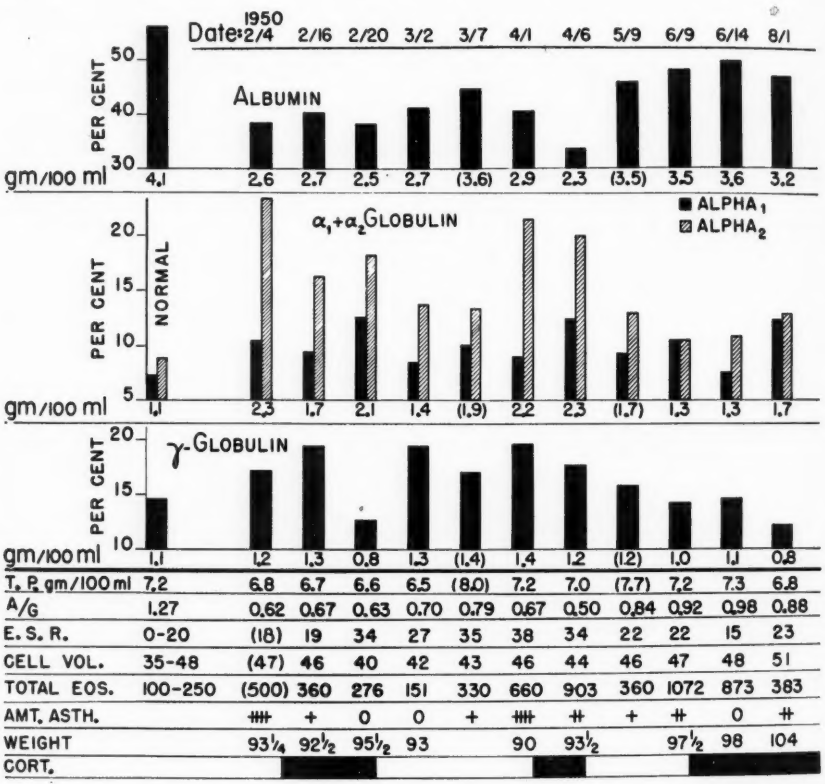

Fig. 1.—Changes in electrophoretic patterns of patient C. Wms. during cortisone treatment.

illustrated in Table VIII. Although the etiology of lupus erythematosus is still obscure, but possibly infective, the improvement of pattern features of lupus sera subsequent to cortisone or ACTH treatment constitutes additional common ground with our observations on pattern improvements in infective asthma.

The rather high incidence of elevated alpha globulin in sera of infective asthma patients (both adults and infants), as well as of children suffering from dermatitis (infantile eczema), recalls a report of Shedlovsky and Scudder,[21] who attributed increased alpha globulin levels of human sera to any

considerable inflammation or tissue destruction irrespective of its cause. Increased alpha globulin levels associated with decreased albumin levels have also been recorded in occasional cases of cirrhosis of the liver[22, 23] and typically in nephrosis.[24-27] In the patients in our studies in whom neither liver nor kidney functions were impaired, increased alpha globulin levels were not related to loss of albumin into the urine or to defective albumin synthesis in the liver but for the present at least they have been assumed to represent the constitutional effect of long-standing chronic infection.

Because of the limited number of cases studied, we present the electrophoretic data from asthmatic children and from patients with dermatitis (both adults and infants) only factually, without attempting interpretation, although the features of the sera from adult dermatitis sufferers seem to indicate that like considerations, as proposed for the serum patterns of adult asthmatic patients, may prevail.

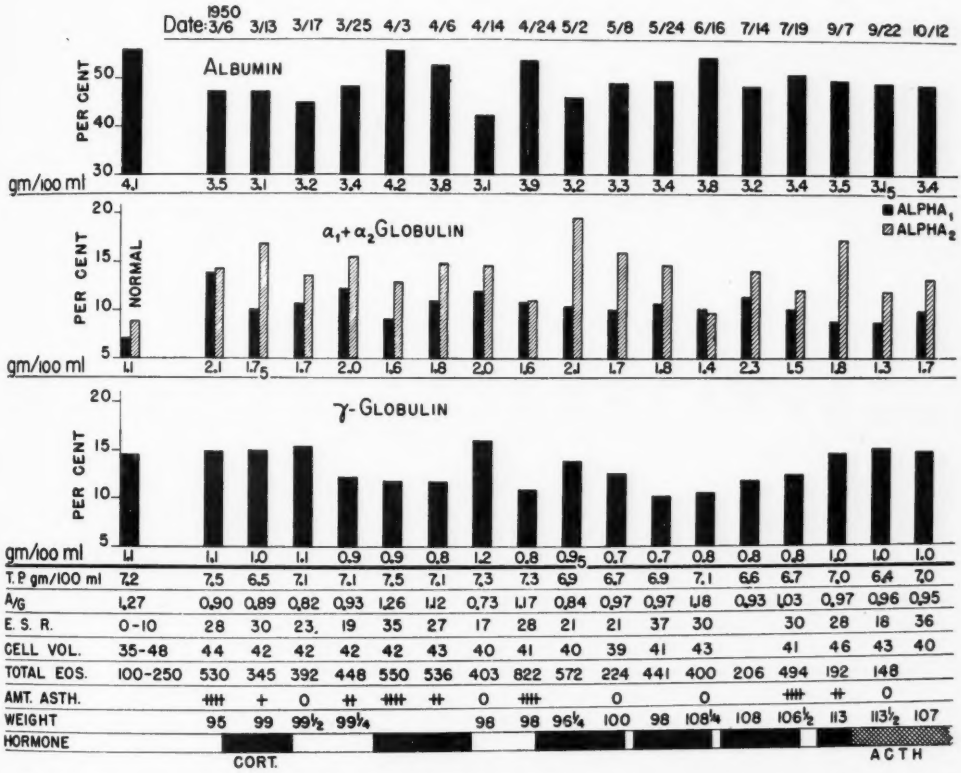

Fig. 2.—Changes in electrophoretic patterns of patient J. Btz. during treatment with cortisone and ACTH.

Studies on Sera During Hormone Treatment.—Numerous serum samples from 4 adult patients suffering from chronic infective asthma were studied electrophoretically before, during, and after completion of hormone treatment. The pattern changes occurring in the course of hormone treatment are presented in Figs. 1, 2, 3, and 4, which also contain additional pertinent data.

TABLE IX. SERUM PROTEIN ANALYSES IN CHRONIC INFECTIVE ASTHMA BEFORE AND AFTER HORMONE THERAPY WITH ELECTROPHORETIC DISTRIBUTION IN PER CENT

PATIENT	SERUMS	DATES	TOTAL PROTEIN BY BIURET (GM./100 ML.) (7.23*)	ALBUMIN (56.0*)	ALPHA$_1$ GLOBULIN (7.2*)	ALPHA$_2$ GLOBULIN (8.8*)	BETA GLOBULIN (13.1*)	GAMMA GLOBULIN (14.7*)	ALBUMIN-GLOBULIN RATIO (1.27*)
J. Btz.	Pretreatment	3/ 6/50	7.5	47.3	13.9	14.3	9.6	14.9	0.90
	During treatment	4/ 3/50	7.5	55.7	9.1	13.0	10.4	11.7	1.26
L. Mse.	Pretreatment	4/10/50	8.5	45.9	13.6	15.5	10.0	15.0	0.84
	During treatment	8/24/50	6.9	55.2	9.2	15.4	7.9	12.3	1.24
C. Wms.	Pretreatment	2/ 4/50	6.8	38.4	10.4	23.5	10.5	17.2	0.62
	During treatment	6/14/50	7.3	49.6	7.6	10.8	17.4	14.7	0.98
L. Pzz.	Pretreatment	4/13/50	6.0	38.6	10.5	19.6	12.5	19.0	0.63
	During treatment	12/11/50	7.0	57.7	5.9	8.0	16.1	12.3	1.36

*Normal values: see Reference 12.

To base definite conclusions on these data obtained from a rather limited number of patients would be premature; however, it may be stated that the serological pictures of all patients who were under prolonged hormone therapy assumed, in all instances, at some stage of the treatment, the features of normal serum patterns or at least approached such features to a definite extent. This is illustrated in Table IX in which the analyses of 4 pretreatment sera are compared with the analyses obtained at the peak of serological improvement, in which respect the highest albumin-globulin ratio encountered in the whole set of analyses was taken as an arbitrary criterion. Particular interest

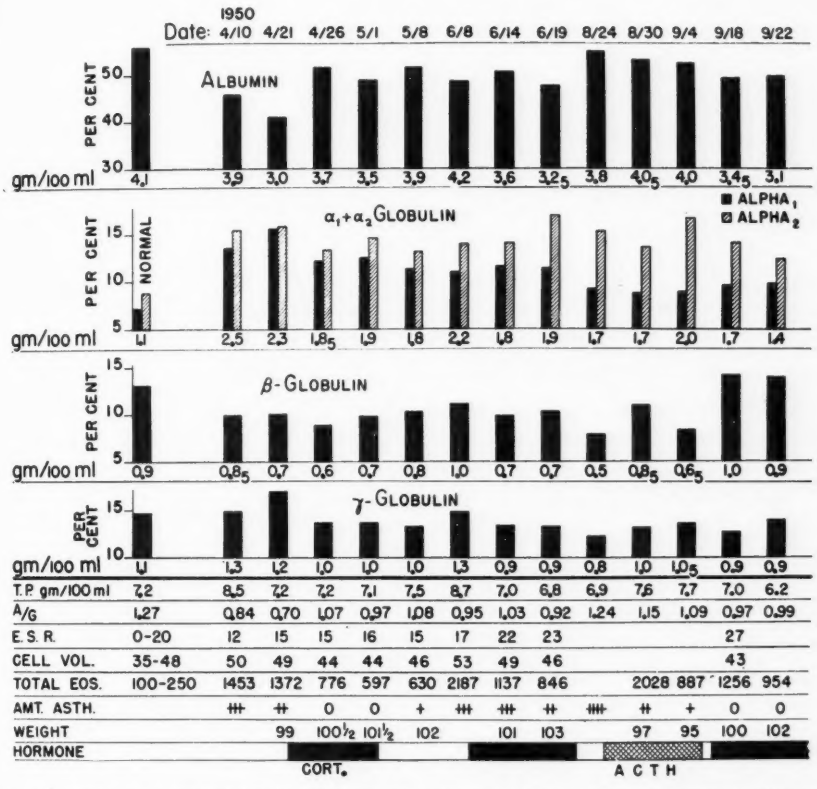

Fig. 3.—Changes in electrophoretic patterns of patient L. Mse. during treatment with cortisone and ACTH.

centers about L. Pzz. (Fig. 4) under continuous hormone therapy with 25 to 50 mg. of cortisone daily for the last 6 months. This 60-year-old patient had severe intrinsic asthma for 7 years. She had pansinusitis, symptoms suggesting periarteritis, occasional pulmonary consolidations, and a large pelvic eosinophilic granuloma. This patient, while free of asthma on August 14, had a total eosinophil count of 1,576. Gradually, over the months, the serum protein distribution returned to normal (Figs. 5, 6, and 7). She has at present only slight asthma at times. Further observations are being made and will be reported in due time. This case introduced the question of the desirability of

moderate but long-continued treatment instead of the short-term intensive use of hormone now prevalent. Improvements such as these, although not as striking, were also noticed in a series of serum analyses of a patient suffering from chronic dermatitis.

To interpret changes in pattern features as being due to direct hormone action would be premature in view of the small number of cases studied. Should serological improvements, such as reported in the diagrams and in Table IX, be consequent (and not only subsequent) to hormone treatment, then the hormone effect on serum would appear to be one of gradual rather than immediate action. Changes immediately subsequent to hormone treatment were occasionally though not regularly observed in these experiments (and other experiments not reported here). As such changes lacked uniformity in their direction, their significance appears to be doubtful. That ACTH has no immediate effect upon the protein distribution of normal sera has been shown by Sayers and associates,[28] and our findings on pathologic sera seem to be, in general, in conformity with these observations, though reservations are as yet in order.

IMMUNOLOGIC STUDIES

The Effect of Hormone Therapy Upon Immediate Wheal Reaction.—It is the immediate concern of every investigator witnessing hormone control of allergic diseases to determine if the beneficial effects could be attributed to interference with the immunologic mechanism, that is the antigen-antibody reaction. Results essentially identical with those recorded in our clinic have been reported already from many sources. Illustrative examples of the various procedures we have used are shown in the following tables. The results with each type of test in from 12 to 15 patients have been monotonously uniform.

TABLE X. COMPARATIVE HISTAMINE REACTIONS BEFORE AND AFTER TEN DAYS OF ACTH THERAPY*

	TESTS BEFORE ACTH†		TESTS AFTER ACTH†	
HISTAMINE DILUTION	WHEAL DIAMETER (CM.)	ERYTHEMA DIAMETER (CM.)	WHEAL DIAMETER (CM.)	ERYTHEMA DIAMETER (CM.)
$1\text{-}10^4$	3.5	6	2.5	6.0
$1\text{-}10^5$	2.0	4	1.8	4.5
$1\text{-}10^6$	1.5	2	1.5	2.6
$1\text{-}10^7$	1.5	1.5	1.2	1.8
$1\text{-}10^8$	1.0	0	1.0	1.6

*ACTH, 25 mg., was given every 6 hours from July 25 to August 6.

†Histamine, 1/10 ml. (1.0 mg. per milliliter), or its serial dilution was injected for each test on the back of patient M. Scz. before (July 24) and on the tenth day (August 3) of ACTH treatment.

Table X records the histamine dilution test giving the diameter of wheal and erythema of each test in a patient who had infective asthma. There are no essential differences in the reactions to histamine in various tenfold dilutions before and after a course of ACTH which had rendered this patient symptom free by the fifth day.

In Table XI are recorded the results of direct tests on a skin-sensitive patient using several antigens to which she reacted. The slight variations noted

TABLE XI. QUANTITATIVE IMMEDIATE SKIN REACTIONS IN A PATIENT TREATED WITH CORTISONE*

ANTIGEN† PROTEIN NITROGEN UNITS‡/ML.	BEFORE CORTISONE 4/13	DURING CORTISONE 4/26	AFTER 11 DAYS OF CORTISONE 5/1	SEVEN DAYS AFTER CORTISONE STOPPED 5/8
Cat dander				
100 units	++	++	+++	+++
10 units	+	+	++	+
1 unit	0	0	0	0
Dog dander				
100 units	+++	+++	+++	+++
10 units	++	+++	+++	++
1 unit	+	+	+	+
1/10 unit	0	0	0	0
Alternaria				
1000 units	+++	+++	+++	++++
100 units	++	+++	+++	+++
10 units	+	++	++	++
1 unit	0	+	+	+
1/10 unit	0	0	0	+

*Cortisone therapy April 21 to May 1.

†Intradermal tests done on patient (L. Mse.) who was sensitive to cat dander, dog dander, and alternaria; 1/10 ml. of antigen injected in each test.

‡One unit = 0.00001 mg. protein nitrogen.

between the tests at the beginning and end of hormone therapy are within the limits of accuracy of the technique of direct testing on 4 separate occasions as was required in this patient.

In a third type of test using the technique of passive transfer, serum was taken from a skin-sensitive patient on different occasions before, during, and after hormone therapy. These sera and their dilutions were injected into sites in the back of a single normal test subject at one time and tested with the appropriate allergen 2 days later. Table XII portrays the results with the serum of patient L. Mse. Variations are apparent, more in this case than some others, but the change in the pretreatment sera compared with the posttreatment sera is not enough to indicate that clinical improvement could be ascribed to a diminution of the humoral skin-sensitizing antibody.

As a final example, an infective but not skin-sensitive asthmatic patient (M. Sez.) was injected with serum from another untreated patient who actively reacted to rabbit dander. Various sites, as explained in Table XIII, were

TABLE XII. TITRATION BY PASSIVE TRANSFER OF THE SKIN SENSITIZING ANTIBODY IN SERA OF PATIENT L. MSE. TREATED WITH CORTISONE*

SERUM OF L. MSE.†	BEFORE 4/10	DURING 4/24	DURING 4/26	END 5/1	AFTER 5/8	SECOND COURSE BEFORE 6/8	SECOND COURSE DURING 6/14
Concentrated	+++	+++	++	+++	++++	++++	++++
1-10	++	++	+	+	++	+++	+++
1-30	+	+	0	0	+	++	++
1-100	0	0	0	0	+	++	++
1-300	0	0	0	0	0	+	+
1-1000	0	0	0	0	0	0	0

*Cortisone therapy, April 21 to May 1 and June 8 to 21 in patient L. Mse.

†One-tenth milliliter of the several serums or their dilutions in physiologic saline solution was placed in each site at one time in same test subject (Pey). Each site was tested 48 hours later by injection of 1/10 ml. of alternaria extract (1,000 protein nitrogen units per ml.) to which patient L. Mse. was very reactive.

TABLE XIII. COMPARATIVE PASSIVE TRANSFER REACTIONS BEFORE AND AFTER 10 DAYS OF ACTH THERAPY* (NONSENSITIVE ASTHMATIC PATIENT M. SCZ.)

RABBIT DANDER SENSITIVE SERUM†	RABBIT DANDER PROTEIN NITROGEN (UNITS/ML.)	REACTION AT 10 MINUTES	
		BEFORE ACTH	AFTER 10 DAYS OF ACTH
Concentrated	500	++++	++++
Concentrated	100	+++	+++
Concentrated	10	++	++
Concentrated	1	+	+
Concentrated	1000	++	++++
1-10	1000	+	+++
1-100	1000	±	++
1-1000	1000	0	±

*ACTH therapy, July 25 to August 6.

†One-tenth milliliter of rabbit dander-sensitive human serum or its dilution in physiologic saline solution was injected into each of the 8 sites on the back of a nonsensitive asthmatic patient (M. Scz.). Three days later each site was injected with 1/10 ml. of rabbit dander extract of the above stipulated strength. Tests were done on July 24 before ACTH and repeated on August 3 after 10 days of ACTH therapy (25 mg. every 6 hours).

made and tested on the third day. She was then given ACTH (100 mg. daily) for 10 days and the same procedure repeated. No important differences appeared in the skin reactions of this patient when sensitized and tested before and later after treatment. This illustrated that the capacity of skin cells to react was not inhibited by the hormone used.

We may summarize these observations on the influence of the hormones on the immediate skin reaction: (1) the response of the skin to histamine was not altered by hormone therapy; (2) the immediate wheal reaction of a sensitive patient to an allergen was not altered by hormone; (3) the serum of skin-sensitive asthmatic patients carried the same degree of sensitizing power after hormone treatment as before; (4) the response of the skin of a nonsensitive asthmatic patient when passively sensitized and tested was not altered by the hormone.

Hence, we may conclude that for the duration and degree of hormone therapy used, the symptomatic benefits from ACTH or cortisone in asthmatic patients were not directly attributable to interference with the immediate wheal type reaction of antigen-sensitized cell as determined in these experiments by the response of the reacting skin or the amount of activity of circulating, skin-sensitizing antibody. However, Bordley,[29] as well as others, has presented evidence of a protection to the respiratory and ocular mucous membrane against air-borne antigen—a paradoxical finding, the reason for which is not clear and deserves further study.

As to the delayed tuberculin-type reaction, several investigators[36] have reported its diminution and disappearance in animals and man under the influence of cortisone or ACTH—a result which might help to explain the good effects of this therapy in the various allergies of infective origin. Further clarification is required here.

The Relation of Skin-Sensitizing Antibody to Gamma Globulin.—During the course of our studies the opportunity arose to review the presence of the skin-sensitizing antibody in the gamma globulin fraction obtained by electrophoresis from sera that carry skin-sensitizing antibody (immediate wheal type

reaction). In previous experiments reported from our laboratory,[30] it had been shown that sensitizing antibody in sera of patients suffering from ragweed hay fever was absent from the albumin and the euglobulin fractions but was present in the pseudoglobulin fraction. The isolation procedure as applied in these experiments, though comprising many steps of precipitation with ammonium sulfate as well as dialyses, was not likely to have led to the isolation of a pure protein entity; probably the pseudoglobulin fraction of these experiments consisted of a mixture of (electrophoretic) alpha and beta globulins together with lesser quantities of gamma globulin. Similar but less clear-cut results were obtained by Scherrer[31] who used either ammonium sulfate or sodium sulfate for precipitating purposes but refrained from purifying the individual fractions.

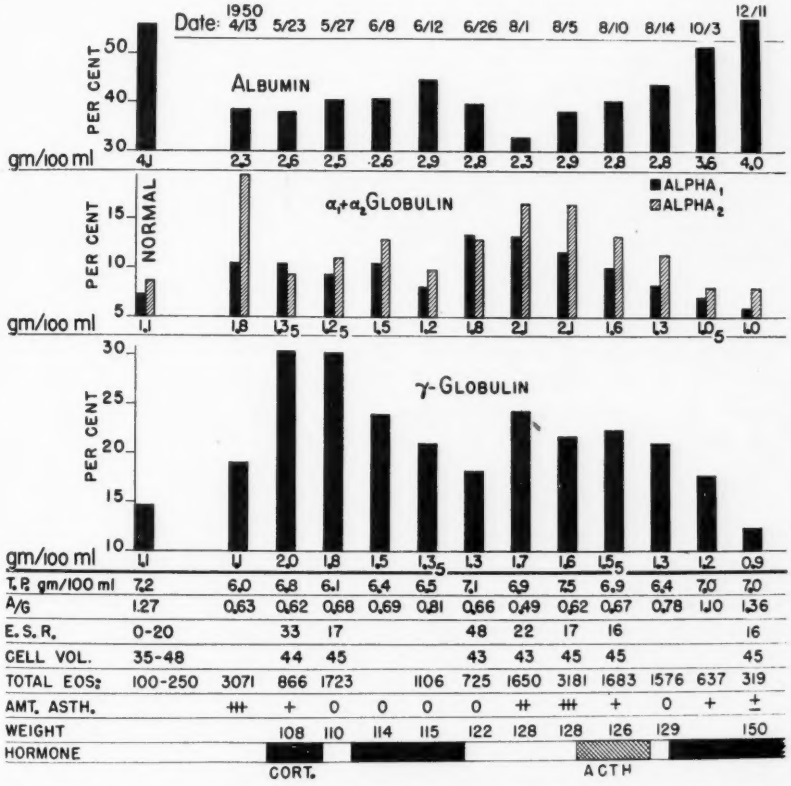

Fig. 4.—Changes in electrophoretic patterns of patient L. Pzz. during treatment with cortisone and ACTH.

The absence of sensitizing antibody in serum albumin has also been reported by Newell and associates,[32] who used an electrophoretic procedure of serum fractionation. They claim to have found sensitizing antibody present in the gamma globulin but absent in the beta globulin fraction. As the electrophoretic equipment then at their disposal lacked essential features of advanced present-day instruments, their conclusions, not yet confirmed, appear to be subject to question or other interpretation. In a recent study of cold

Fig. 5.

Fig. 6.

Fig. 7.

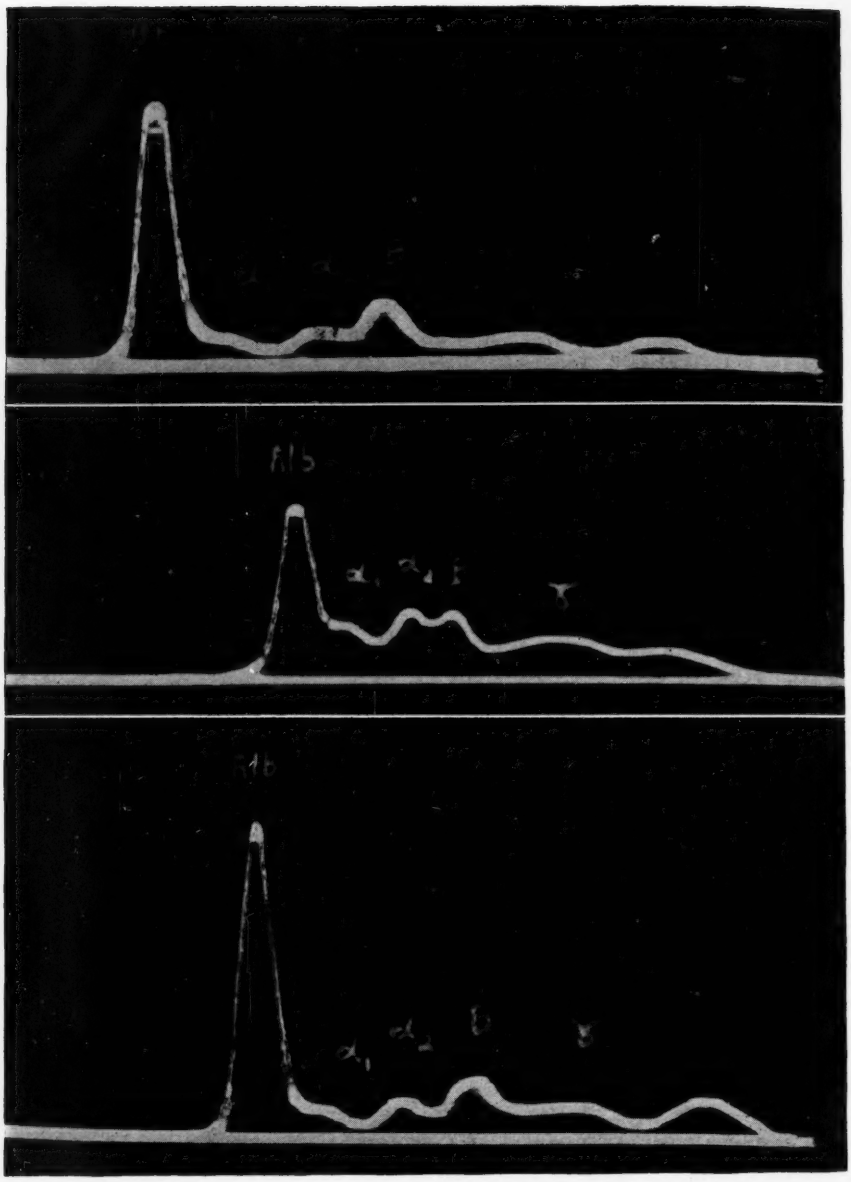

Fig. 5.—Electrophoretic pattern of normal serum.
Fig. 6.—Electrophoretic pattern of serum of patient L. Pzz. before treatment.
Fig. 7.—Electrophoretic pattern of serum of patient L. Pzz. after treatment with cortisone and ACTH.

sensitivity by Sherman and Seebohm,[33] electrophoretic fractionation of serum was employed. For reasons which are given they stated, "Definite conclusions as to which of the protein components of the serum were involved in the reaction are impossible. However, it appeared that transfer of cold sensitivity depended upon the presence of more than one component in contrast to the transfer of ragweed pollen sensitivity which was accomplished with pure gamma globulin."

More recently Campbell and associates[37] have reported the presence of skin-sensitizing activity in alpha and beta globulin fractions of allergic sera, as separated by the electrophoresis-convection method.

We have lately analyzed, by the electrophoretic method, numerous human sera transferring the immediate skin-sensitizing antibody (wheal type). We did not find the gamma globulin concentration uniformly elevated and encountered several sera whose gamma globulin concentrations were within, or even at, the lower limits of the normal range. Prompted by these observations, we entered upon some preliminary studies in order either to confirm or to disprove these claims. Such studies seemed to be the more warranted in view of some reports in the literature[34, 35] of the association of antibody with electrophoretic globulin components other than gamma globulin (or components migrating at mobilities intermediate between beta and gamma globulin).

Our procedure in these preliminary studies was briefly as follows: serum known to contain skin-sensitizing antibody was subjected to electrophoresis. The end component of the descending limb, that is, gamma globulin, was collected and its protein concentration estimated, refractometrically, in most instances. A sample of the original serum whose total protein content had been determined colorimetrically and whose gamma globulin content, electrophoretically was diluted with saline solution to the same gamma globulin concentration as that of the separated gamma globulin for comparative passive transfer tests. Also the collected serum portion contained in the bottom section of the electrophoretic cell was likewise adjusted, as well as serum diluted with barbiturate buffer and dialyzed against barbiturate buffer prior to electrophoresis. In this manner 4 solutions of comparable gamma globulin concentration were obtained, namely: (1) serum neither alkalinized with barbiturate buffer nor subjected to electrophoresis, (2) serum alkalinized with and dialyzed against barbiturate buffer but not subjected to electrophoresis, (3) serum alkalinized with and dialyzed against barbiturate buffer and exposed to the electric current during electrophoresis, and (4) electrophoretically isolated gamma globulin of presumably high purity. It should be stated that the barbiturate solution used is not irritating when injected intracutaneously as required in our tests. These 4 primary solutions were further diluted with saline solution either in threefold or in fivefold steps and passive transfer tests according to the Prausnitz-Küstner technique were performed. Such experiments should show whether barbiturate buffer with or without subsequent exposure to the electric current during electrophoresis (but without separation of the serum constituents) would effect any alteration of the titer as compared with the titer of the original serum. No essential difference, however, was observed.

Under these circumstances, isolated gamma globulin would have shown reactivity to the same extent as the other 3 serum dilutions, provided all of the sensitizing antibody was associated with gamma globulin. This was not the case in any of the 10 tests performed on various transferring sera, the titer of the isolated gamma globulin fractions being in every instance about 10 times lower than the titer of the other serum dilutions, Table XIV.

TABLE XIV. PASSIVE TRANSFER REACTIONS OF GAMMA GLOBULIN COMPARED WITH WHOLE SERUM, DIALYZED SERUM, AND MID-PORTION SERUM PROTEINS

PATIENT, SERUM*	TESTED WITH ANTIGEN	WHOLE SERUM†	DIALYZED SERUM	MID-PORTION SERUM PROTEINS	GAMMA GLOBULIN
A. Tsd.	Alternaria				
Concentrated		+++	+++	+++	+
1-5		+	+	+±	0
1-15		0	0	±	0
1-50		0	0	0	0
J. Dgl.	Cat dander				
Concentrated		+++	+++	+++	+++
1-5		++	+++	+++	++
1-15		++	++	++	±
1-50		+	++	+	0
1-150		0	+	+	0
1-500		0	±	±	0
1-1500		0	+	0	0
P. Bdn.	Ragweed				
Concentrated		++	++	++	±
1-5		+	+	+	+
1-15		+	+	+	0
1-50		+	±	±	0
1-150		0	0	0	0
N. Csn.	Cat dander				
Concentrated		+++	Not done	+++	+++
1-5		+++		+++	+++
1-15		+++		+++	++
1-50		++		++	+
1-150		+		+	0
1-500		±		+	0
1-1500		0		0	0
V. Stn.	Dog dander				
Concentrated		+++	+++	+++	+++
1-3		++	++	++	++
1-10		++	++	+	++
1-30		+	+	+	0
1-100		+	+	+	0
1-300		0	0	0	0

*One-tenth milliliter of serum, dialyzed serum, mid-portion, or gamma globulin or their stipulated dilutions was injected in each site on the back of normal test subjects and tested 2 days later with 0.025 ml. of designated extract in each site and read after 20 minutes.

†Serum diluted so that the gamma globulin content was quantitatively the same as in the dialyzed serum, the mid-portion, and the separated gamma globulin.

Although we are fully aware that in these preliminary experiments cumulative estimated errors of ± 50 per cent may be involved, it seems to be unlikely that the regularly encountered lower titers of gamma globulin were due to possible experimental errors. As our experiments rather seem to indicate that the bulk of sensitizing antibody is not associated with gamma globulin, we have engaged in experiments to confirm these preliminary results by more exacting techniques and to investigate whether the bulk of sensitizing antibody may be found to be associated either with one or the other of the electro-

phoretically obtainable serum globulins or whether a synergistic action of 2 or more serum constituents is necessary to account for the reaction of sensitizing antibody in the passive transfer tests.

GENERAL SUMMARY

1. A clinical study of the effects of ACTH and cortisone in several allergic diseases—asthma, dermatitis, and urticaria—has demonstrated a favorable symptomatic effect in practically all cases during their administration, but there is little lasting effect when the causative factor continues to operate. Hence, a study for the cause in all chronic cases is as imperative as it ever was. The value of a temporary respite, however, must not be minimized and the benefits to be derived from prolonged continuation therapy have not yet been adequately explored.

2. Serologic studies have been carried out using chemical and electrophoretic techniques on patients with chronic infective asthma and intrinsic dermatitis. The patterns in many sera have shown distinctly abnormal distribution of the various protein fractions, albumin, alpha$_1$, alpha$_2$, beta and gamma globulins. Comparative studies have suggested that these changes are not the result of the allergic state, per se, but appear to be related directly or indirectly to the chronic underlying infection since similar alterations of protein distribution are found in such chronic nonallergic infections as osteomyelitis and bronchiectasis. These changes are even comparable to the profound changes recorded by Reiner[20] in lupus erythematosis.

3. Immunologic studies indicate that the symptomatic benefits and tissue alterations resulting from hormonal therapy with ACTH and cortisone are not due to interference with the immediate wheal type reaction of antigen-antibody sensitized cells.

It was further observed that the skin-sensitizing antibody of allergic sera is not wholly contained in the gamma globulin fraction of such sera.

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CUTANEOUS REACTIONS TO STAPHYLOCOCCUS POLYSACCHARIDE, PROTEIN, AND AN UNFRACTIONATED EXTRACT IN HYPERSENSITIVE AND NORMAL INDIVIDUALS*†

MORTON C. KAHN, D.Sc., HORACE S. BALDWIN, M.D., BENJAMIN R. ZEITLIN, M.S., AND MARILYN SMART, B.S., NEW YORK, N. Y.

BECAUSE of the frequent occurrence of staphylococci in foci of infection of persons demonstrating clinical allergic symptoms,[1] it has been conjectured that these organisms might, in some hypersensitive individuals, be concerned with the mechanism of this complicated syndrome.[2] In order to ascertain the existence of an etiological relationship, it would be desirable to obtain an extract of the whole staphylococcus and relatively pure staphylococcus fractions which would possess significantly greater specific activity in cutaneous tests on allergic, as compared to normal, individuals.

Various attempts have been made to demonstrate the nature of the cutaneous response to staphylococci using bacterial extracts and fractions of unstated criteria of purity. Stevens and Jordan[3] reported the immediate and delayed responses to cutaneous tests made with nucleoprotein obtained from staphylococci and other respiratory microorganisms on 100 asthmatic patients. Swineford and Holman,[4] utilizing fractionated bacterial nucleoprotein and polysaccharide derived from staphylococci and other organisms, observed a high incidence of both the immediate and delayed response in cutaneous tests made with their fractions. The fractions employed by both groups of investigators were admittedly crude and no comparison of the incidence of the cutaneous reactions to staphylococcus fractions in normal and allergic individuals was reported.

This report describes the procedures which were followed to obtain immunologically noncross reactive staphylococcus fractions, and demonstrates the results obtained from cutaneous tests of these derivatives on normal and allergic persons.

Materials and Methods.—A bacteriologic study was made of the flora of the upper respiratory tract of asthmatic patients. Staphylococci were found to predominate in the sinus, nose, and polyp cultures. The locales from which materials were taken for culturing were the sinuses, polyps, throat, sputum, and bronchoscopic fluid. The materials, obtained from the clinic, were streaked on horse blood agar plates which were examined at 24 and 48 hour intervals. Colonies were selected, and subcultured into differential media.

Ten strains of staphylococci recovered from these plates were chosen for fractionation. Organisms F 10 thru H 1 (see Table I) were mannitol fermentive and coagulase positive, criteria which correlate for over 90 per cent of pathogenic staphylococci.[5] These strains consisted of staphylococci which were hemolytic, nonhemolytic as well as aureus, citreus, and albus in pigmentation. A coagulase negative and mannitol negative strain of staphylococcus (F 7)

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†Department of Public Health and Preventive Medicine, Cornell University Medical College, and the New York Hospital, Department of Medicine, Allergy Division.

TABLE I. CULTURAL CHARACTERISTICS OF 10 STRAINS OF STAPHYLOCOCCI ISOLATED FROM ASTHMATIC PATIENTS

STRAIN	SOURCE	BLOOD AGAR (REACTION IN DAYS)	LITMUS MILK (REACTION IN DAYS)	GELATIN (REACTION IN DAYS)	COAGULASE (REACTION IN DAYS)	MANNITOL (REACTION IN DAYS)	GLYCEROL (REACTION IN DAYS)	SALICIN (REACTION IN DAYS)	ORGANISM
F 10	Antral membrane	Hemolytic aureus 1	Acid 2, coag. 2*	+ 6	+ 1	+ 3	+ 8	+ 20	*Staphylococcus aureus* (hemolytic)
F 11	Antral membrane	Hemolytic citreus 1	Acid 3, slight coag. 6	+ 6	+ 1	+ 8	0	0	*Staphylococcus citreus* (hemolytic)
B 7	Antral membrane	Slightly hemolytic aureus 1	Acid 9, lysis 9, slight coag. 10	+ 8	+ 1	+ 7	+ 10	0	*Staphylococcus aureus* (slightly hemolytic)
B 9	Throat	Slightly hemolytic aureus 1	Acid 9, slight coag. 9	+ 8	+ 1	+ 7	+ 13	0	*Staphylococcus aureus* (hemolytic)
W 2	Throat	Nonhemolytic aureus	Acid 1, coag. 6	+ 20	+ 1	+ 7	+ 13	+ 20	*Staphylococcus aureus* (nonhemolytic)
W 5	Throat	Nonhemolytic aureus	Acid 1, coag. 6	+ 20	+ 1	+ 7	+ 13	+ 20	*Staphylococcus aureus* (nonhemolytic)
V 2	Throat	Hemolytic albus 1	Acid 3, coag. 6	+ 6	+ 6	+ 8	+ 13	+ 8	*Staphylococcus phary.* (hemolytic)
V 3	Throat	Hemolytic albus 1	Acid 3, coag. 6	+ 6	+ 6	+ 9	+ 9	+ 8	*Staphylococcus phary.* (hemolytic)
H 1	Throat	Slightly hemolytic aureus 1	Acid 2, coag. 2	+ 8	+ 1	+ 7	+ 7	0	*Staphylococcus aureus* (slightly hemolytic)
F 7	Sputum	Nonhemolytic albus	Acid 3 coag. 28	0 46	0	0	+ 14	0	*Staphylococcus epidermidis* (nonhemolytic)

\+ = positive reaction
0 = no reaction
All strains positive to the following tests:

Inulin tests negative
H_2S
Dextrose
maltose
sucrose
lactose
raffinose
inulin 0
$NO_3^- = NO_2$

was included for the purpose of observing the comparative effects of fractions derived from pathogens and nonpathogens on the incidence of the cutaneous reaction. Inasmuch as little is known of the variation in ability of various strains of staphylococci to induce the wheal and flare reaction in hypersensitive individuals, it appeared advisable to include a number of these strains in order to compare their mean level of reactivity on groups of patients and controls.

A modification of the Verway procedure[6] was adapted as the method of fractionation in preference to that of Julianelle and Wieghard,[7] because of the relatively mild, undenaturing operations entailed in the fractionation procedure and for the ability to yield purified polysaccharide, protein, and nucleoprotein fractions, immunologically noncross reactive.

Four fractions were isolated for each of the 10 strains of staphylococci. Using Verway's nomenclature for these fractions, there were obtained (1) a fraction termed AI and AII composed of nucleoprotein; (2) fraction B, a purified type-specific protein; (3) fraction C, a purified polysaccharide, and (4) fraction R, a crude extract of water-insoluble, alkali-soluble bacterial nucleoprotein residue. Fraction R was included in these tests to observe the comparative effect of a crude nucleoprotein fraction on the incidence of the delayed cutaneous reaction. We also included an unfractionated water-soluble extract of the ground staphylococcus strain F 10, made as follows:

An 18 to 24 hour nutrient broth culture of staphylococcus was Sharples centrifuged at about 20,000 r.p.m. and washed 5 times with physiologic saline solution, and each washing was followed by centrifugation. The organisms were lyophilized and the dry mass ground at 8° C. in a refrigerated ball mill equipped with glass beads. The grinding process lasted for 96 hours or until very few intact cells were observed microscopically. The ground mass was then taken up in a buffered physiologic salt solution, pH 7.0, as suggested by Evans,[8] omitting the phenol. It was extracted for 24 hours at 8° C. and followed by centrifugation at 2,000 r.p.m. for 3 hours. The supernatant solution was then filtered through a sterile Seitz filter. A staphylococcus extract obtained from bacteria grown in 50 L. of culture media contained an average of 57,000 Cooke-Stull units per milliliter.

Modification of the Verway Procedure.—Unlike the Verway method, separation of the C fraction from fraction B was accomplished by ultrafiltration through the use of a 3.0 per cent Parlodion* coated Alundum thimble. This concentration of Parlodion was found capable of filtering the polysaccharides and retaining the protein B fraction. Fraction B was then precipitated with trichloracetic acid as outlined in the original procedure.

Ether extraction of the C fraction was omitted. Instead, the solutions were concentrated by vacuum distillation at 18 to 20° C., and the distillates trapped in a dry ice alcohol bath. Alcoholic precipitation of the polysaccharide in the residue was then accomplished as originally outlined.

In our purification procedures we substituted negative pressure dialysis where electrodialysis was suggested.

*Mallinckrodt Chemical Works, St. Louis, Mo.

TABLE II. PRECIPITIN REACTIONS OF ANTIGENS AND ANTISERA DERIVED FROM STAPHYLOCOCCUS F 10

STAPHYLOCOCCUS F 10 ANTISERA TO:	NUCLEOPROTEIN FRACTION AI			NUCLEOPROTEIN FRACTION AII			TYPE-SPECIFIC PROTEIN FRACTION B			CRUDE RESIDUE FRACTION R			POLYSACCHARIDE FRACTION C			UNFRACTIONATED EXTRACT			SALINE CONTROL
	U*	1/10	1/100	U*	1/10	1/100	U*	1/10	1/100	U*	1/10	1/100	U†	1/10	1/100	U*	1/10	1/100	
A I		++	-	+++	+++	+	?	0	0	+++	+++	0	0	0	0	+++	++	0	0
A II	+	+++	++	+++	+++	++	0	0	0	+++	+++	0	0	0	0	+++	+++	0	0
B	0	0	0	0	0	0	++	+++	0	?	0	0	0	0	0	+	++	0	0
R	+++	++	0	+++	+++	++	?	0	0	+	+++	+	+	+++	0	+++	+++	0	0
C	0	0	0	0	0	0	?	0	0	?	0	0	0	0	0	+	0	0	0
Unfractionated extract	0	0	0	+	?	0	+	+	0	+	+	0	+	+	0	+	+	0	0
Vaccine	++	+	+	++	+++	++	++	++	0	+++	+++	++	+	+++	+	++++	++++	+++	0
Normal serum control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

U* = Antigen concentration: approximately 50 mg. per cent N.
U† = Antigen concentration: approximately 50 mg. per cent polysaccharide.
0 = No precipitin formation.
? = Doubtful or trace.
+ = Slow forming; definite precipitate at 48 hours.
++ = Definite immediate precipitate.
+++ = Heavy precipitate.
++++ = Extremely heavy precipitate.
Observed after 1 hour in incubator at 37° C., and at 24 and 48 hours at 8° C.
All sera negative to antigens at 1:1000 dilution.
Milliliters of sera used for test—0.2 ml.
Milliliters of antigen used for test—0.2 ml.

The organisms used for these tests were treated with 5 washings of physiologic saline solution followed by repeated centrifugation before proceeding with the lyophilization process.

Chemical Criteria of Purity.—(1) With the polysaccharide fractions, negative Millon, xanthoproteic, ninhydrin, and Hopkins-Cole reactions were obtained. The biuret tests were considered negative since they matched egg albumen diluted 1:2,000, which is the limit of delicacy. Heavy metal salts, such as $AgNO_3$, $PbC_2H_3O_2$, $HgCl_2$; salts, such as $(NH_4)_2\ SO_4$, NaCl, or $K_4Fe\ (CN)_6$; and acids, such as trichloracetic, sulfosalicylic, and acetic resulted in no precipitation. The Molisch tests were strongly positive; Fehling tests were negative but positive after HCl hydrolysis. Lugol's iodine test for starch was negative. (2) For the protein fraction B, the Molisch test produced very faint positive reactions. Bial tests were negative, Fehling tests were negative and after HCl hydrolysis, negative. Protein tests were all positive. (3) Fractions AI and AII contained the bulk of the bacterial nucleoprotein and thus exhibited positive protein and carbohydrate reactions.

Immunologic Criteria of Specificity.—To evaluate the immunologic specificity of the various fractions, a representative pathogenic strain, F 10, was fractionated and 5.0 ml. containing 50 mg. N per 100 ml. of each protein fraction injected intravenously into rabbits at intervals over a period of 21 days. (For the C fraction, 50 mg. per 100 ml. was used.) After a 7 day rest period the rabbits were bled and the sera collected. Similar procedures were followed using a heat-killed staphylococcus F 10 vaccine and an unfractionated extract of this organism. Immunologic homologous and cross-precipitin reactions were undertaken using the serial antigen dilution method.

From Table II, it is seen that fraction AI and AII are mutually cross reactive. They were therefore combined for skin testing. Fraction B was highly specific, showing no reaction or only doubtful trace reactions in the most concentrated antigen dilutions with heterologous fractions. Fraction C, the polysaccharide fraction, demonstrated no reactivity with the sera of fraction AI, AII or B. A serum made from fraction C showed only doubtful or trace reactions with fractions B and R, and a slow-forming precipitate to the unfractionated extract. Fraction C antigen did, however, form a slow-forming precipitate with antisera to the unfractionated extract and strong reactions with antisera to the vaccine and crude fraction R. Thus, fraction C was not capable of eliciting the formation of antibodies but is able to produce precipitates with rabbit sera prepared from the whole organism or from unfractionated extracts or crude fractions thereof.[6, 7]

Solutions of the fractions and whole extract were prepared in physiologic saline solution in concentrations of 100 Cooke-Stull units for the protein fractions and 1:100,000 dilution for the polysaccharides. These were arbitrarily considered low enough in concentration to minimize nonspecific reactions.[9] No preservatives were added. The solutions were Seitz filtered and tested for sterility. Preliminary tests for toxicity were performed by intravenous and cutaneous inoculations in rabbits and by cutaneous tests on 5 human volunteers with no untoward results. The protein fractions and unfractionated extract

were analyzed for protein N by phosphotungstic acid precipitation and Kjeldahl N determination preceding the skin tests and at intervals of 6 weeks thereafter, with no appreciable loss in protein N content. Similarly, stability tests were applied to the C fraction using the quantitative Molisch test and Hagedorn-Jensen method for determination of reducing sugars.

The response to the cutaneous tests were grouped as negative, weak, and strong reactions. Where occasional nonspecific reactions to administered saline controls occurred, only those reactions which were 1.0 cm. larger than that exhibited by the saline were measured. Weak reactions were those with small wheals not over 0.5 cm. diameter and having variable radii of erythema. Strong reactions were considered those having wheals over 0.5 cm. in diameter and exhibiting erythema wider than 1 cm. in radius. In the compilation of per cent positive reactions, both weak and strong reactions were combined.

Two groups were chosen for the experiment. The first group consisted of 134 ambulatory clinic patients with 277 allergic and related conditions. Their complaints are listed in Table III. No one patient, however, was subjected to

TABLE III. CLINICAL MANIFESTATIONS IN 134 AMBULATORY CLINIC PATIENTS

	NO. OF CONDITIONS
Bronchial asthma	72
Hay fever	81
Allergic dermatitis and eczema	6
Miscellaneous	
Chronic sinusitis	41
Vasomotor rhinitis	32
Polyps	9
Chronic tonsillitis	10
Deviated septa	6
Bronchitis	6
Bronchiectasis	3
Emphysema	8
Chronic otitis media	1
Angioneurotic edema	1
Physical allergy to cold	1
Total	277

all of the tests. The second group was composed of 25 medical students in good health with no allergic complaints. Some of the student controls had histories of previous minor staphylococcus infections.

To compare the data, results were compiled in terms of the number of clinic patients who were positive per 100 clinic patients tested, and also, in terms of positive reactions obtained per 100 tests administered. Statistical analyses by Chi^2 were performed on each compared set of values to determine whether or not there was a significant relationship between them not accountable to chance.

VARIATION IN THE ABILITY OF STAPHYLOCOCCUS FRACTIONS AND UNFRACTIONATED EXTRACT IN ELICITING THE IMMEDIATE CUTANEOUS REACTION

Table IV, A and B, summarizes the results of the immediate cutaneous tests observed in the clinic patients and controls to the 9 strains of pathogenic staphylococci.

In Table IV, A, values are presented as per cent positive reactions for the fractions of each strain of staphylococcus tested and the Chi² obtained for the mean of each set of values is given.

TABLE IV. THE IMMEDIATE CUTANEOUS REACTION

*A. Per Cent Positive Reactions**

STAPHYLOCOCCUS STRAIN	FRACTION C		FRACTION AI AND II		FRACTION B		FRACTION R	
	CLINICAL PATIENTS (PER CENT)	CONTROL (PER CENT)	CLINICAL PATIENTS (PER CENT)	CONTROL (PER CENT)	CLINICAL PATIENTS (PER CENT)	CONTROL (PER CENT)	CLINICAL PATIENTS (PER CENT)	CONTROL (PER CENT)
F 10	38.4	0	23.1	8	28.5	16	10.3	16
B 7	7.7	0	11.5	8	14.3	24	3.4	8
F 11	42.3	20	0	4	0	8	13.8	16
V 2	34.6	0	7.7	8	14.3	20	20.7	16
W 5	19.2	12	7.7	0	25.0	4	24.1	20
B 9	38.5	8	7.7	12	NT†	4	10.3	16
V 3	26.9	8	11.5	20	14.3	12	6.9	20
H 1	0	0	7.7	4	21.4	16	6.9	8
W 2	3.8	0	NT†	4	25.0	8	NT†	8
Average per cent positive reactions	23.5	5.4	9.6	7.6	17.9	12.4	12.0	14.2
Number of tests administered	234	225	208	225	224	225	232	225
Chi² n = 1	$\chi^2 = 13.2$		$\chi^2 = 0.5$		$\chi^2 = 3.0$		$\chi^2 = .08$	

B. Clinic Patients and Controls Revealing Positive Reaction for 9 Strains of Pathogenic Staphylococci

	FRACTION C		FRACTION AI AND AII		FRACTION B		FRACTION R	
	PATIENTS	CONTROLS	PATIENTS	CONTROLS	PATIENTS	CONTROLS	PATIENTS	CONTROLS
Number patients tested	26	25	26	25	28	25	29	25
Positive patients and controls	19	8	10	10	14	9	10	10
Positive patients and controls (per cent)	73.1	32.0	38.5	40.0	50.0	36.0	34.5	40.0
Chi² n = 1	$\chi^2 = 8.6$		$\chi^2 = 0.01$		$\chi^2 = 1.24$		$\chi^2 = 0.17$	

*Protein fractions tested at 100 Cooke-Stull units; Fraction C tested at 1×10^{-5} Gm. ml.

†Not tested.

Summary of the per cent of positive immediate reactions to the 9 strains of pathogenic staphylococci elicited in the clinic patients and controls.

An individual was considered to be positive only once for a given fraction even though he may have been sensitive to more than one strain of staphylococci.

In Table IV, B, the number and per cent of clinic patients and controls in whom weak and strong reactions were elicited is tabulated and the Chi² obtained for each of the sets of values is given.

From the average of the values obtained in Table IV, A and B, it appears that in approximately similar numbers of clinic patients and controls positive cutaneous reactions to the protein fractions were elicited. With the polysaccharide fraction C, however, the clinic patient group evoked reactions far in excess of the controls: 23.5 per cent positive tests as compared to 5.4 per cent,

and the number of patients positive, 73.1 per cent as compared to 32.0 per cent for the controls: $Chi^2 = 13.2$ for the per cent positive reactions, and $Chi^2 = 8.6$ for the per cent patients and controls in the polysaccharide fraction. Both Chi^2 values are considered highly significant.

An additional indication of the clinic patients' reactivity to the C fraction is demonstrated in Table V, showing the multiple reactions to each fraction, that is, through a compilation of patients and controls showing sensitivity to more than one strain for each fraction.

TABLE V. PER CENT OF CLINIC PATIENTS AND CONTROLS SHOWING MULTIPLE REACTIONS

NUMBER OF REACTIONS	FRACTION C		FRACTION AI AND AII		FRACTION B		FRACTION R	
	CLINIC PATIENTS (PER CENT)	CONTROLS (PER CENT)	CLINIC PATIENTS (PER CENT)	CONTROLS (PER CENT)	CLINIC PATIENTS (PER CENT)	CONTROLS (PER CENT)	CLINIC PATIENTS (PER CENT)	CONTROLS (PER CENT)
0	26.9	68	61.5	60	50.0	64	65.5	60
1	23.1	20	19.2	28	17.8	12	13.8	12
2	15.4	8	3.9	4	10.8	4	0	8
3	7.7	4	11.5	0	3.6	8	10.35	8
4	15.4	0	3.9	8	3.6	0	0	4
5	0	0	0	0	7.1	4	10.35	4
6	7.7	0	0	0	7.1	8	0	4
7	3.8	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0
9	0	0	—	0	—	0	—	0
Per cent patients and controls demonstrating 2 or more reactions per fraction	50.0	12	19.3	12	32.2	24	19.7	28

These results demonstrate that the greatest number of multiple reactions were elicited to the C fraction by those in the clinic patient group. The clinic patient group thus appeared to exhibit a greater cutaneous sensitivity to many more strains of staphylococcus polysaccharide than did the control group. Both patients and controls, however, showed relatively similar levels of reactivity to multiple strains of the protein fractions.

It was of interest to observe the immediate cutaneous reactivity to the fractions of a nonpathogenic staphylococcus strain, F 7, tested on the clinic patients. The results are demonstrated in Table VI.

An average of 11.8 per cent positive cutaneous reactions were elicited by the fractions of the nonpathogenic strain, F 7, as compared to an average of

TABLE VI. NONPATHOGENIC STAPHYLOCOCCUS F 7; POSITIVE IMMEDIATE REACTIONS ON CLINIC PATIENTS*

FRACTION	TESTS ADMINISTERED	TOTAL POSITIVE REACTIONS	POSITIVE REACTIONS (PER CENT)
C	36	7	19.4
AI & II	36	2	5.6
B	36	4	11.1
R	36	4	11.1

*Student controls were not available when these tests were administered.

15.7 per cent positive reactions among the clinic patients tested with the 9 pathogenic staphylococci. From these results, it would seem that among hypersensitive individuals the urticarial reaction may not necessarily be limited to the pathogenic strains alone, but can be demonstrated to appear, though at a lower level of reactivity, in tests made with a nonpathogenic strain.

The immediate cutaneous response of a physiologic, unfractionated, saline extract of ground staphylococcus (F 10 strain) diluted to 100 Cooke-Stull units resulted in positive responses in 47.7 per cent of the clinic patients and 20.0 per cent of the controls. The Chi^2 value obtained is 6.77.

Kraft, Mothersill, and Nestmann,[10] reporting the immediate skin reactions to a commercially prepared staphylococcus extract (U.B.A., Eli Lilly & Company), also found a high incidence in the immediate reaction among allergic persons and a low order of response among normal controls. However, the utilization of such extracts gives no indication of the fractions possibly involved in the mechanism of this syndrome.

VARIATION IN THE ABILITY OF STAPHYLOCOCCUS FRACTIONS IN ELICITING THE DELAYED CUTANEOUS REACTION

Table VII summarizes the results of the delayed cutaneous response to the 9 pathogenic strains of staphylococci.

It has been conjectured by Swineford and Holman[4] that "Tests with purer bacterial fractions would emphasize or minimize the observed tendency for the polysaccharides to elicit the immediate and for the nucleoprotein to elicit the delayed reactions." We observed that the delayed reaction to all fractions occurred with much less frequency than did the immediate reaction. Among the clinic patients, protein fraction B, which produced the greatest number of immediate protein reactions, also elicited the highest incidence of delayed reactions of all the fractions tested. Twenty-eight per cent of the patients and 10.5 per cent of the tests administered showed the delayed reaction to protein fraction B. The control group to this fraction evoked, however, a low order of response to this substance; 8.0 per cent of controls and 0.9 per cent of the tests showed the delayed response.

Similar numbers of patients and controls demonstrated the delayed reaction to the nucleoprotein fraction AI and II and to crude fraction R. Although crude nucleoprotein fraction R produced a somewhat greater number of reactions than the fraction AI and II, the increase was not sufficiently large to warrant any conclusion.

The polysaccharide C fraction evoked the lowest incidence of delayed reaction of any of the fractions. In 225 tests on 25 controls with the 9 polysaccharide fractions, no delayed response occurred. Of 198 skin tests with these same fractions on the clinic patients an average of 2 per cent delayed responses resulted; 13.5 per cent of the patients tested elicited this type of reaction.

The delayed cutaneous reactions to the fractions of the nonpathogenic strain F 7, tested on the clinic patients, showed results that paralleled that of the 9 pathogenic strains.

TABLE VII. SUMMARY OF DELAYED REACTIONS ELICITED BY 9 PATHOGENIC STAPHYLOCOCCI; PER CENT POSITIVE DELAYED REACTIONS

STAPHYLOCOCCUS STRAIN	FRACTION C		FRACTION AI AND II		FRACTION B		FRACTION R	
	CLINIC PATIENTS (PER CENT)	CONTROLS	CLINIC PATIENTS (PER CENT)	CONTROLS	CLINIC PATIENTS (PER CENT)	CONTROLS	CLINIC PATIENTS (PER CENT)	CONTROLS
F 10	4.5	0	4.8	0	8	0	0	0
B 7	0	0	4.8	0	4	0	0	0
F 11	4.5	0	0	0	4	0	0	0
V 2	0	0	0	4	8	4	0	4
W 5	0	0	0	0	12	0	5	4
B 9	9.1	0	0	0	*	0	0	0
V 3	0	0	9.5	4	12	0	0	0
H 1	0	0	9.5	0	24	4	20	12
W 2	0	0	*	4	12	0	*	0
No. tests performed	198	225	168	225	200	225	160	225
Average of per cent positive reactions	2.0	0	3.6	1.3	10.5	0.9	3.1	2.2
No. patients tested per strain	22	25	21	25	25	25	20	25
Average per cent positive clinic patients and controls	13.6	0	14.3	8.0	28.0	8.0	20.0	16.0

Protein fractions = 100 Cooke-Stull units; Polysaccharide fractions = 1×10^{-5} Gm. ml.
*Not tested.

It would appear then too, from the tendency observed here, that a general lowering of the incidence of delayed cutaneous reactivity occurred as compared to the higher incidence of the immediate reaction. Particularly interesting is the absence of the delayed reaction to the polysaccharide C fraction among the controls.

DISCUSSION

The fact that a similarity of response exists in the immediate cutaneous test to each of the protein fractions and that wide disparity exists to the C fraction among the hypersensitive patients as compared to the controls would lead one to conjecture as to the possibility of a relationship between staphylococcus polysaccharide and staphylococcus hypersensitivity. Although it might be expected that the clinic patient group would be subject to a higher incidence of staphylococcus infection due to the exacerbating effects of allergy and asthma on infections of the upper respiratory tract, it would be reasonable to expect an all around higher incidence of reactivity to all of the fractions. That this was not the case is demonstrated by the findings.

The possibility exists that these polysaccharides have practical application as diagnostic test materials in the cutaneous wheal and flare reaction for staphylococcus-induced allergy. The use of these polysaccharides for desensitization of persons allergic to staphylococci is also contemplated.

Whether the immediate response to the polysaccharide C fraction is due to the existence of an immune state or to allergy can only be settled through

further investigation. Such information may be derived from a correlation of clinical symptoms with the presence of circulating antibodies for staphylococcus polysaccharides in hypersensitive persons and controls. The use of the Prausnitz-Küstner technique and Schultz-Dale reaction, will also aid in determining the significance of this substance in its relation to the syndrome of staphylococcus hypersensitivity.

As an explanation for the increased cutaneous activity of the staphylococcus polysaccharide fraction, and the unfractionated extract among the allergic patients, it may be conjectured that there is a low percentage of individuals revealing skin-sensitizing antibodies among the normal population as contrasted to the hypersensitive group. This is in line with the well-known tendency for atopic individuals to develop sensitivity to house dust and other antigens such as pollens and epidermals to which they have been exposed as compared with nonatopic individuals. So far as bacterial allergy is concerned, it is interesting to compare these results with staphylococcus polysaccharide with those obtained by Heidelberger and Avery,[11] Tillett and Francis[12] and by Finland and Dowling[13] in their studies of the pneumococcus capsular polysaccharide. They demonstrated that some pneumococcus polysaccharides precipitate antipneumococcus sera, produce shock in sensitized animals, and give an immediate urticarial reaction in pneumonia convalescents while producing a low incidence of urticaria on cutaneous injection in normal individuals. Mehlman and Seegal[14] and Chase[15] have also shown that cutaneous sensitization to pneumococcus polysaccharide was capable of being passively transferred.

CONCLUSION

1. In cutaneous tests made on hypersensitive individuals and normal controls, utilizing an unfractionated extract, polysaccharide, protein, and nucleoprotein fractions derived from 9 strains of pathogenic staphylococci by a modification of the Verway procedure, we were able to elicit a high incidence of immediate wheal and flare reactions similar to those produced by common allergens in atopic individuals.

2. Staphylococcus extract and staphylococcus polysaccharide are capable of eliciting a significantly greater incidence of wheal and flare reactions in hypersensitive as compared to normal individuals.

3. Within the scope of our survey we have been able to demonstrate that the immediate cutaneous reactions to staphylococcus protein and nucleoprotein fractions are not limited to hypersensitive individuals but are produced, although in somewhat lesser proportion, in normal adults as well.

4. No one strain of staphylococcus among the 9 pathogenic strains tested appeared more outstanding than another in its ability to induce the immediate reaction with the various fractions although variations in that ability for individual fractions did occur. We used such strains as *Staphylococcus albus, Staph. aureus,* and *Staph. citreus* in forms which were hemolytic and nonhemolytic in our tests. These strains were all coagulase positive and mannitol fermentive. A strain of nonpathogenic staphylococcus *(Staph. epidermidis)*

which was coagulase negative and mannitol negative, induced reactions in a somewhat lesser proportion of hypersensitive individuals tested.

5. A low incidence of the delayed reaction to all the staphylococcus fractions was observed as compared to that obtained for the immediate cutaneous response. Particularly interesting was the absence of the delayed response to the polysaccharide C fraction among the controls.

6. The high incidence of immediate reactions to staphylococcus extract and staphylococcus polysaccharide in hypersensitive individuals as compared with controls suggests a tendency for atopic individuals to develop sensitivity to staphylococci similar to that prevalent among these individuals with respect to inhalants and other common allergens.

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ELECTROCARDIOGRAPHIC CHANGES IN EXPERIMENTAL ANAPHYLACTIC REACTIONS*

GEORGE MIKULICICH, M.D., LOS ANGELES, CALIF.

IT IS a well-established fact that anaphylactic or allergic reactions in experimental animals, especially in rabbits, result in tissue changes which are spread throughout the body, chiefly localized around blood vessels. The early observations of the processes were accomplished in experimental study by Ashoff,[1] Klinge,[2] Vaubel,[3] Junghans,[4] and others.

It is not the purpose of this paper to summarize the literature on this subject. Such summarizing reviews are numerous.[5-10] Later this problem of hypersensitivity-tissue reaction in rabbits and its similarity with rheumatic tissue changes in human beings was elaborated by Rich, Lewis, and Wintrobe,[11] Rich,[12-14] and Gregory and Rich.[15-18] Sensitizing rabbits with horse serum or white egg albumin, they obtained tissue changes around the vessels in many organs, especially in the heart muscle. These were similar in some of the animals to the Ashoff nodules found in human rheumatic disease. The variabilities of the individual reactions among the animals have been emphasized in the reports of former experimental studies. Some animals showed tissue reactions which paralleled those noted in periarteritis nodosa of human pathology. Many more animals showed tissue reactions than those which reacted with general anaphylactic shock. For example, in the report of Rich and Gregory,[15] 14 rabbits were sensitized with 10 c.c. of horse serum per kilogram, and only 3 died immediately after the second injection of the antigen due to acute anaphylactic shock.

Observations, to be published later, on over 100 rabbits which were sensitized chiefly with horse serum as a part of a study of the relationship of nervous systems to specific hypersensitivity, revealed the following facts:

1. Only about 10 per cent succumbed to immediate death in acute general anaphylactic shock.
2. The typical manifestations which occurred in a sensitized rabbit upon further large antigen injection were: (a) the almost complete temporary disappearance of the precipitin antibody titer in serum, following large dosage of antigen, and (b) the temporary disappearance of the skin reactivity to antigen (Arthus phenomenon), even when large amounts of antigen are used for this intracutaneous test. According to the present theoretical concept, it is assumed that each time that a certain amount of antigen is injected the biochemical reaction between the antigen and the aggregating antibody takes place in the serum as well as within the tissue cells (especially smooth musculature and other mesenchymal cells).

*From the Department of Pharmacology, Stritch School of Medicine of Loyola University.

The biochemical reaction provokes a "cell injury" and seems to be partially due to the release of histamine, heparin, acetylcholine, choline, adenosine, lysocythin, and probably other not yet known substances of en-

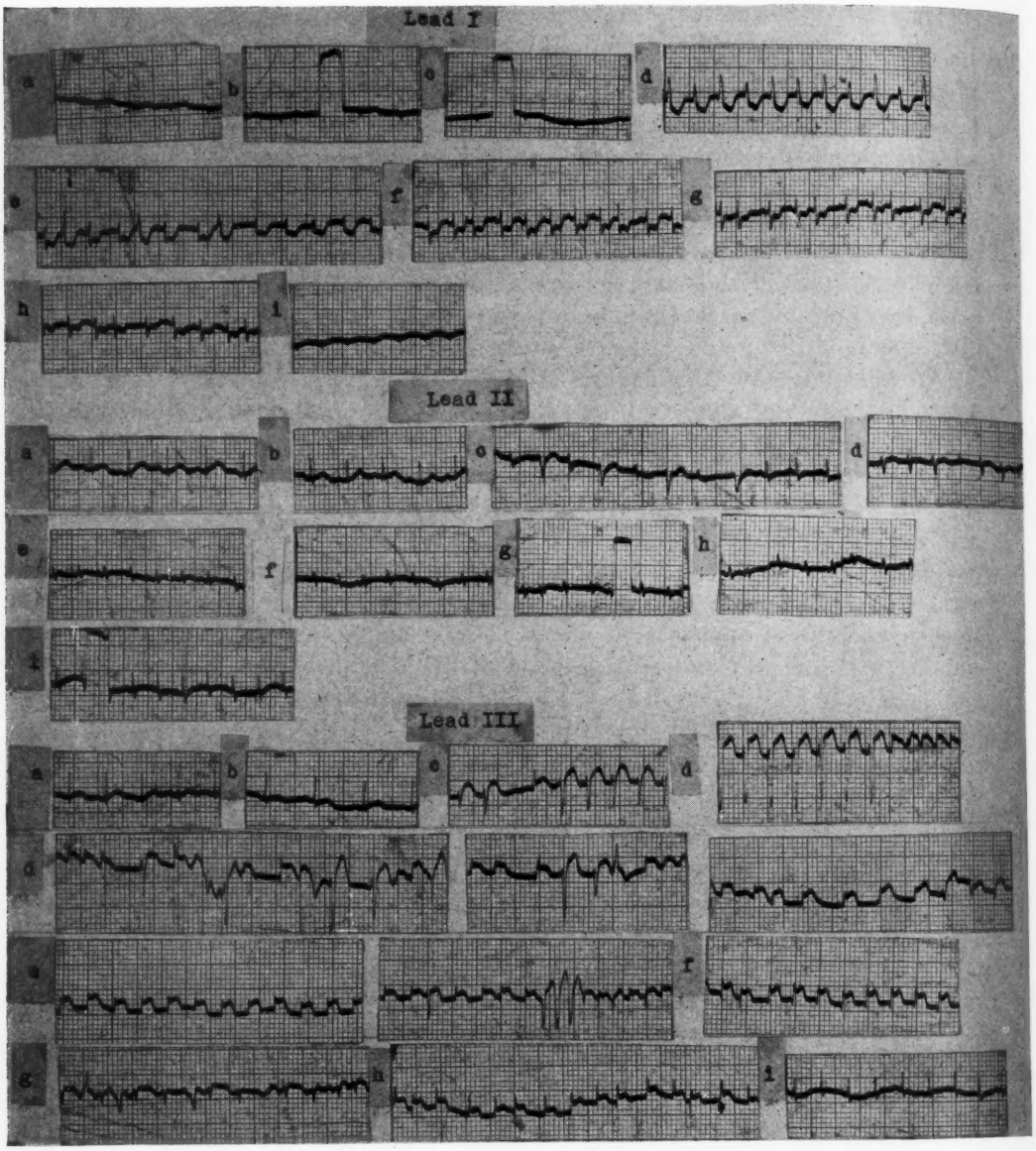


Fig. 1.—Electrocardiogram of Rabbit SE-2 (male, 1,700 Gm.) made on June 6, 1950, 17 days after first sensitization with horse serum, 5 c.c. per kilogram intravenously. *a*, Before injection of horse serum, 3 c.c. intravenously; *b*, during 1 minute after injection; *c*, 1.30 to 3.20 minutes after injection; *d*, 3.30 to 5 minutes after injection; *e*, 7 to 9 mintues after injection; *f*, 10.30 to 11.50 minutes after injection; *g*, 15 to 16.30 minutes after injection; *h*, 20 to 21 minutes after injection; and *i*, 45 minutes after injection.

During the recording time there was no sign of shock. Death occurred spontaneously on June 10, 1950. Microscopic examination showed diffuse and nodular interstitial myocarditis of the heart (see photomicrograph, Fig. 2) and serous exudation (foci of pneumonitis) of the lung.

zymatic nature, for instance, the hypothetic slow-acting substance. The activation of serum protease (trypsin, plasma protease, and so on) by a substance released by the disintegration of thrombocytes and leucocytes is also supposed to be in some way connected with the chain of biochemical reactions involved in the anaphylactic process.[19] Further assumption involves the acceptance of the fact that one molecule of an antigen can bind many molecules of antibody.[8] Thus it would seem likely that an amount of antigen over 5 c.c. per kilogram would be sufficient to bind all the antibodies present in the circulation and the tissue of a rabbit. In contrast to these biochemical processes, anaphylactic shock as previously mentioned is an infrequent expression of an

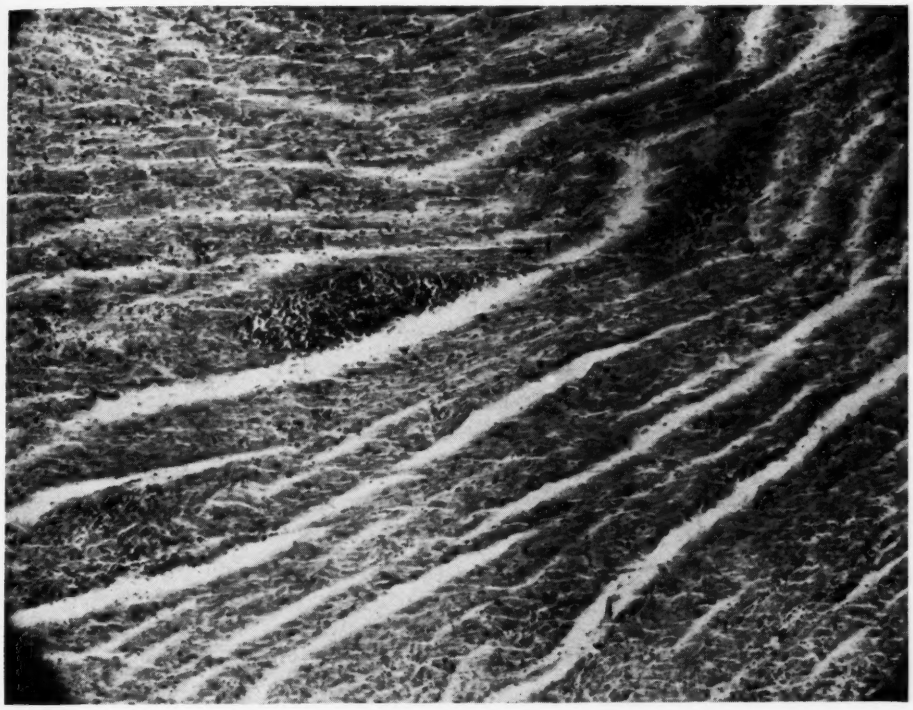


Fig. 2.—Photomicrograph of heart muscle of Rabbit SE-2 showing nodular infiltration of the heart muscle.

antigen antibody reaction (in the rabbit). The experimental experience that the heart and lung tissue reactions are those which are chiefly involved in the antigen-antibody phenomena in rabbits indicated that a study should be made of the electrocardiographic changes which occurred during the antigen-antibody reaction in vivo.

Our review of the literature disclosed the paucity of studies in which electrocardiographic observations were made in experimental anaphylaxis. The only reports, seemingly generally neglected, dealing directly with this problem were those of Auer and Robinson[20] and Robinson and Auer.[21] The former paper describes electrocardiographic findings in 24 rabbits sensitized with several subcutaneous injections of horse serum and shocked 4 weeks later

with intravenous injection of 9 ml. horse serum in total. Eleven rabbits of this group were previously bilaterally vagotomized. The fatality rate in this study was high, since 10 of 24 animals succumbed in fatal anaphylactic shock. The latter paper embraces similar experimental studies in dogs. In this experiment only electrocardiographic records with the second lead were used. This may explain the failure of these studies to demonstrate the most typical pattern changes which are primarily and prominently expressed in the first and third leads, as to be described.

METHODS AND RESULTS

In unanesthetized rabbits electrocardiographic recordings were taken immediately, before, and after the injection of the horse serum antigen* for a period up to one-half hour. (The electrocardiograms were taken on a Sanborn Viso Cardiette, except that in several experiments a simultaneous record of all 3 leads was taken with the Polycord Electrocardiograph.)

The technique used for securing the electrocardiograms was to place the rabbit in an appropriate wooden box and affix the electrodes by means of safety pins through the skin. The pins were soldered to a wire which was attached to the leads of the electrocardiograph.

Electrocardiograms were taken from 28 rabbits selected at random from the previously mentioned 100 animals. Of these 28 selected rabbits, 4 were sensitized with egg albumin alone, 2 with horse serum and egg albumin, and 22 were sensitized with only horse serum. Some of the 22 rabbits were sensitized with 5 ml. of horse serum per kilogram, and the remainder with 10 ml. of horse serum per kilogram. Only 2 rabbits showed slight and short-lasting electrocardiographic changes after the first injection, that is, the sensitizing injection of horse serum. This was noted in an animal which received a sensitizing dose of 10 ml. per kilogram of the serum, and in 1 which received 5 c.c. per kilogram.

Both rabbits which showed electrocardiographic changes after the first injection of horse serum died 1 to 4 days after this injection. Autopsy of one of these animals, a female 3 weeks after parturition, showed slight coccidiosis and fatty infiltration of the liver, as well as pronounced hypertrophy of the suprarenal gland and small scars of the myocardium.

Of the 6 animals which received egg albumin, 2 gave slight and short-lasting electrocardiographic changes after the first injection of the egg albumin. These 6 animals received 10 ml. per kilogram of egg albumin (Merck) administered as a 10 per cent solution.

Fourteen to 17 days after the first injection of horse serum the second injection was administered intravenously with a total dosage from 0.1 to 10 ml. per kilogram. Pronounced and prolonged electrocardiographic pattern changes were obtained invariably even with dosage as low as 0.1 ml. per kilogram.

In addition, all the 6 rabbits sensitized with egg albumin demonstrated a similar type of electrocardiographic pattern changes when exposed to the

*Horse serum without preservatives was kindly supplied by the E. R. Squibb & Sons, New York, N. Y.

second intravenous injection of 10 per cent egg albumin in dosages of 5 ml. per kilogram 14 to 17 days after initial sensitization.

These heart reactions which were noted starting from one-half to 3 minutes after termination of the injection were usually initiated by a more or less pronounced short period of bradycardia, which was followed by a tachycardia, frequently with a previous interposition of various types of extrasystoles. A deep depression of the ST_1 phase appeared, followed by an enlargement of the QRS wave in time and especially in voltage with a T inverted to R prominently expressed in first and third leads. Very characteristic was the appearance of the inversion of enlarged QRS wave in the third lead, indicating an acute left deviation and during some periods resembling a branch block. Contrary to the pronounced ST depression in the first lead an elevated monophasic coronary ST in the third lead usually appeared for a period of time (one to several minutes), resembling the pattern of the acute coronary infarction in human beings (see Figs. 1 and 3).

Other changes which usually appeared with various intensity include ventricular extrasystoles of various types; auricular fibrillation; and periods of branch block resembling, as mentioned, a Wilson block with interference due to extrasystoles. All these alternating changes usually lasted for a period of 3 to 15 minutes after the injection of the antigenic substance. All these most characteristic features of the elecrocardiographic pattern changes were, as mentioned, prominently expressed in the first and third leads.

When a general anaphylactic shock occurred the electrocardiographic pattern changes were usually interrupted by a period of extreme bradycardia frequently as slow as 15 to 20 beats per minute. After this short interruption the typical pattern might recur again for 2 to 4 minutes under shock conditions, turning over in case of fatality into premortal electrocardiographic changes of the dying heart.

Most of the 28 rabbits did not show a general reaction following the injection of the antigen and during the course of pronounced heart reaction recorded with electrocardiographic pattern changes. Some of them were noted to be slightly cyanotic, but behaved quietly. This contrast we may further emphasize with the fact that the second injection of horse serum administered 14 to 17 days after the sensitization resulted without exception in pronounced electrocardiographic changes even when small dosages of horse serum as antigen were used.

In some of the 28 animals electrocardiographic changes were repeatedly demonstrated after several injections of horse serum generally administered at intervals of 14 to 17 days. All these reactions were similar and typical in their electrocardiographic pattern but varying in time and intensity. Occasionally the fifth or sixth injection of horse serum failed to demonstrate a typical reaction. However, subsequent injections after the usual period of 14 to 17 days with large amounts of horse serum as antigen resulted, in some of these animals, in a reappearance of typical electrocardiographic patterns, but of a short duration and lower intensity. The presence or absence of these

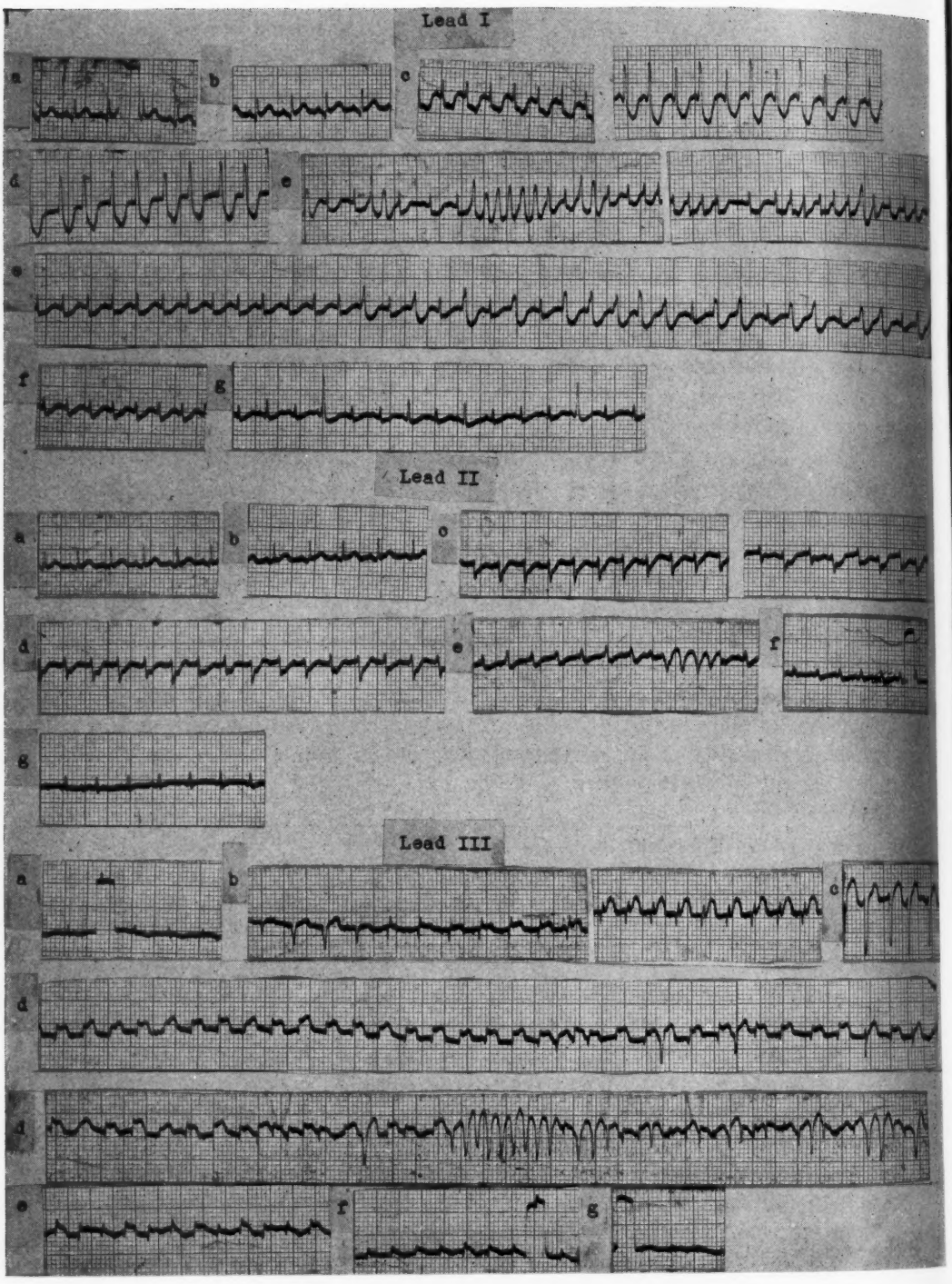


Fig. 3. (*For legend, see opposite page.*)

electrocardiographic changes after the fifth or later injection was not correlated with the level of precipitin titer of the serum.

In 4 rabbits which received the second shocking injection of horse serum under deep general anesthesia with Nembutal (35 mg. per kilogram intra-

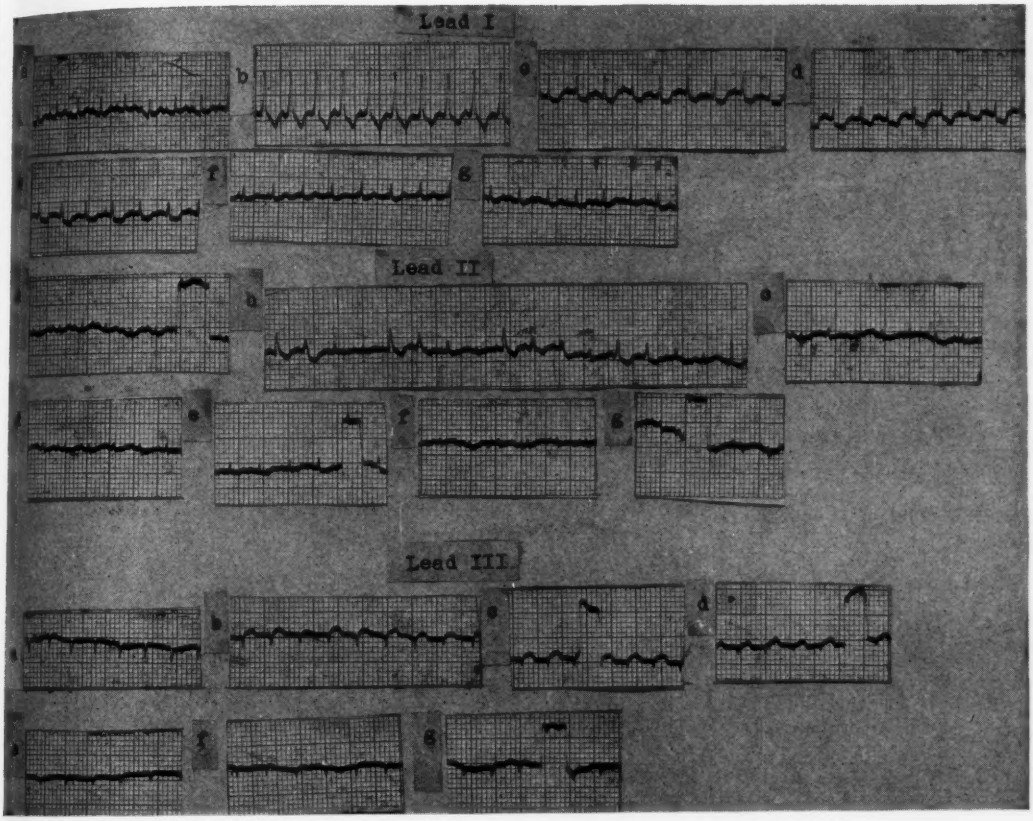


Fig. 4.—Electrocardiogram of Rabbit Z-1 (male, 3,500 Gm.) made on Mar. 1, 1950. The first sensitization was done Feb. 11, 1950, with horse serum, 10 c.c. per kilogram intravenously. Precipitin titer on Feb. 20, 1950, was 1:5,000, and on March 1 it was 1:10,000. The second horse serum injection (4 c.c. intravenously) was given Mar. 1, 1950. *a*, before injection of 4 c.c. horse serum; *b*, 1 to 2 minutes after injection; *c*, 3 to 4 minutes after injection; *d*, 5 to 6 minutes after injection; *e*, 7 to 8 minutes after injection; *f*, 11 to 12 minutes after injection; and *g*, 22 minutes after injection.

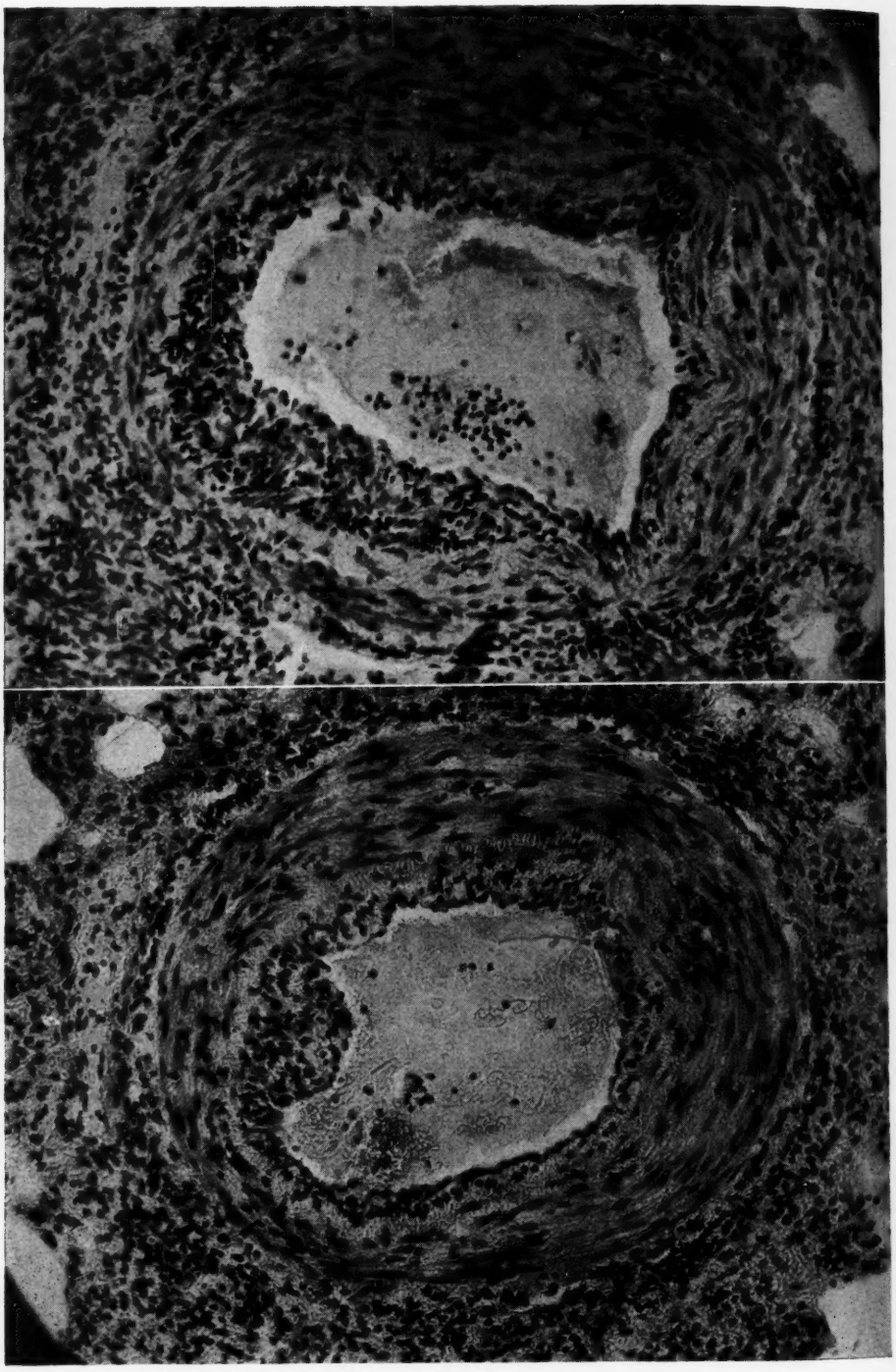
The third horse serum injection on Mar. 6, 1950, with 10 c.c. per kilogram intravenously in Nembutal anesthesia (30 mg. per kilogram intravenously) did not show any electrocardiographic changes. Precipitin titer was 1:10,000. Death occurred spontaneously on Mar. 13, 1950.

Microscopic examination showed cellular infiltration especially pronounced in the subepicardial region of the heart. In the liver there was hepatitis in foci, and cellular infiltration around the vessels. There was atelectasis of the lung with serous exudation and intima proliferation of the lung vessels (see photomicrograph, Fig. 5). Foci of interstitial nephritis were present in the kidney.

Fig. 3.—Electrocardiogram of Rabbit 83 (albino male, 2,400 Gm.) made May 4, 1950. First injection of horse serum, 5 c.c. per kilogram intravenously, was given April 21, 1950, and a second injection of horse serum, 1 c.c. per kilogram intravenously, was given May 4, 1950. Precipitin titer was 1:10,000. *a*, Before intravenous injection of horse serum, 1 c.c. per kilogram; *b*, during 1 minute after injection; *c*, 1½ to 3 minutes after injection; *d*, 3 to 5 minutes after injection; *e*, 5 to 8 minutes after injection; *f*, 10 to 11 minutes after injection; and *g*, 17 to 18 minutes after injection.

The animal was sacrificed on May 10, 1950. Microscopic examination showed that interstitial proliferation of the heart was not very pronounced. Arteritis of the coronary branches of the papillary muscles was present. There was arteritis of several small lung vessels. Perivascular proliferation of the liver was present but not very pronounced.

A.

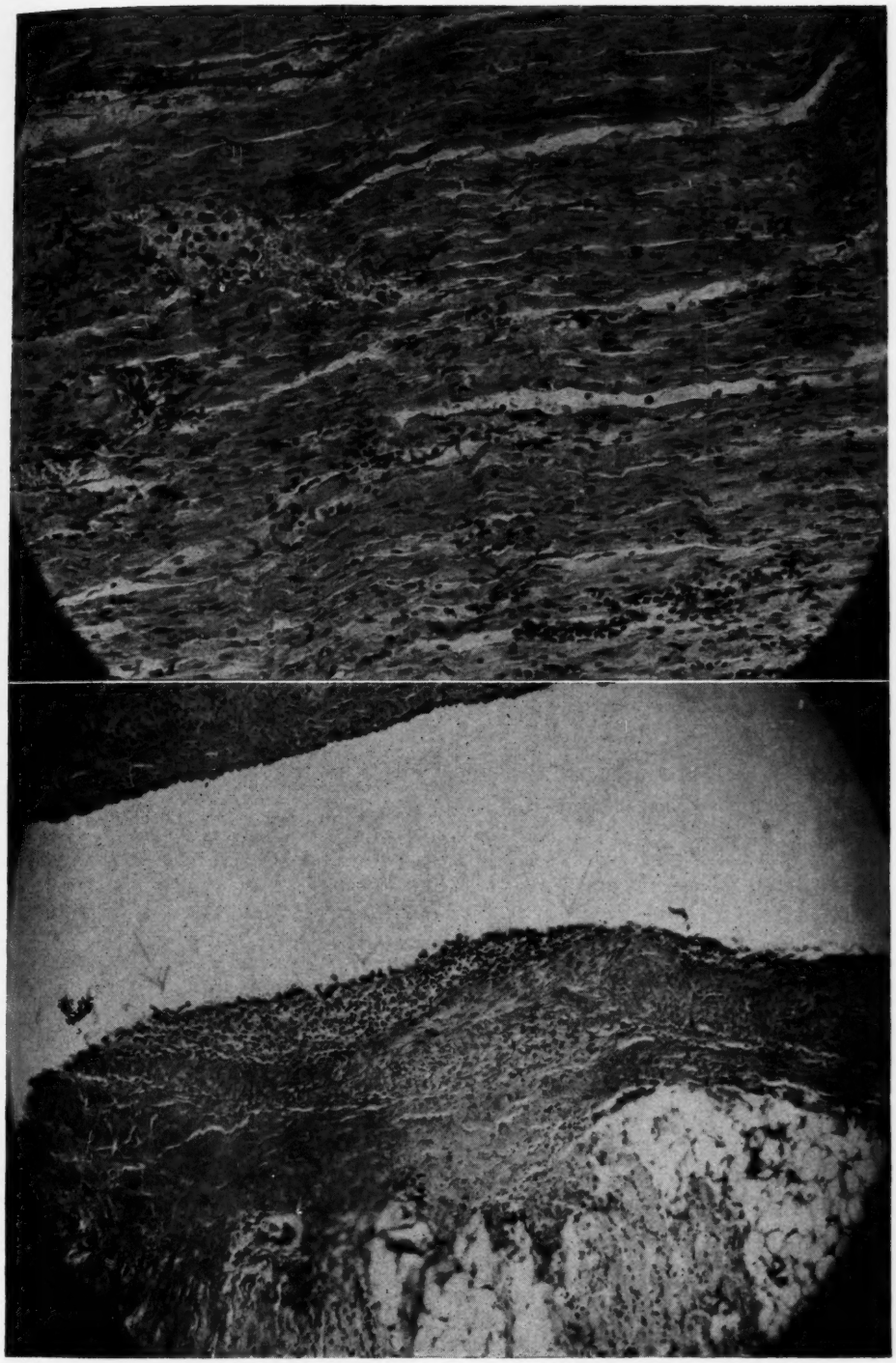


B.

Fig. 5, *A*.—Photomicrograph of Rabbit Z-1. Arterial vessel of the lung in different sections with marked intima proliferation (endarteritis).

Fig. 5, *B*.—Same artery as in Fig. 5, *A*, another section.

C.



D.

Fig. 5, *C.*—Interstitial proliferation and small nodular infiltration in the myocardium.
Fig. 5, *D.*—Cellular infiltration of the subendocardial area below the aortic valves.

venously), typical electrocardiographic changes were noted and interrupted with interference due to a general lethal shock (see Fig. 6). However, in 3 of 5 rabbits under similar anesthesia these electrocardiographic pattern changes following third or fourth horse serum injections were not obtained. They were also absent when the second injection was given in fractional dosage of 0.05 ml. horse serum per kilogram diluted with several milliliters of physiologic solution 4 to 5 times during 15 to 20 minutes.

When the electrocardiographic pattern changes subsided after injection of horse serum, even with dosages as small as 0.1 ml. per kilogram, further horse serum injections given one-half to several hours later, even with large dosages such as 10 ml. per kilogram, failed to elicit any changes in the electro-

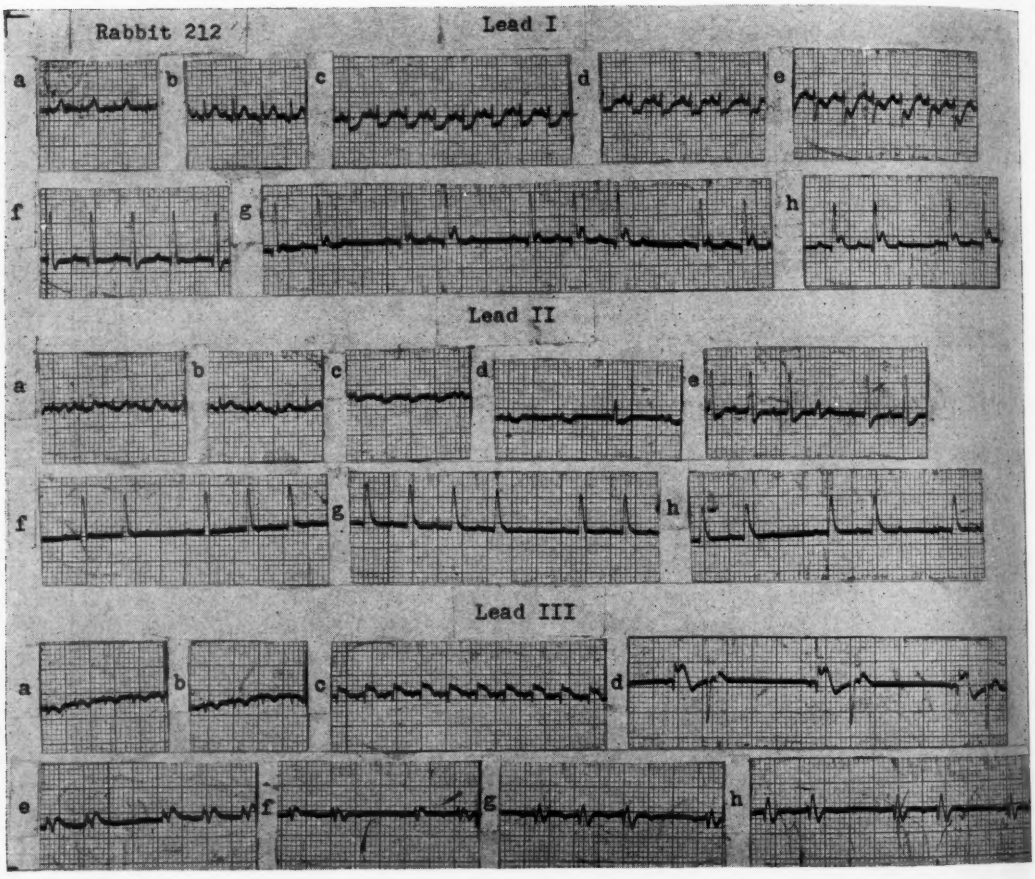


Fig. 6.—Electrocardiogram of Rabbit 212 (male, 2,220 Gm.) made on Sept. 15, 1950. The first horse serum injection, 3 c.c. per kilogram intravenously, was given Aug. 28, 1950. The second injection of horse serum, 5 c.c. per kilogram intravenously under 35 mg. per kilogram of intravenous Nembutal anesthesia, was given Sept. 15, 1950. *a*, Before anesthesia; *b*, 12 minutes after the injection of Nembutal, 35 mg. per kilogram intravenously; *c*, 0 to 1 minute after injection of horse serum, 5 c.c. per kilogram intravenously; *d*, 1 to 2 minutes after injection (shock with cessation of respiration beginning 1 minute after the injection); *e*, 3 to 6.30 minutes after injection; *f*, 6.50 to 7.35 minutes after injection; *g*, 8.20 to 9.20 minutes after injection; and *h*, 10 to 10.30 minutes after injection.

The animal died. The electrocardiographic pattern is typical until *f*, and from there on atrioventricular dissociation is manifested with QRS changes due to the dying heart.

cardiogram. This was a regular observation and no exceptions were noted in 10 such subsequent repeated injections.

The accompanying figures which illustrate the electrocardiographic pattern changes have been taken from several experiments and selected for dem-

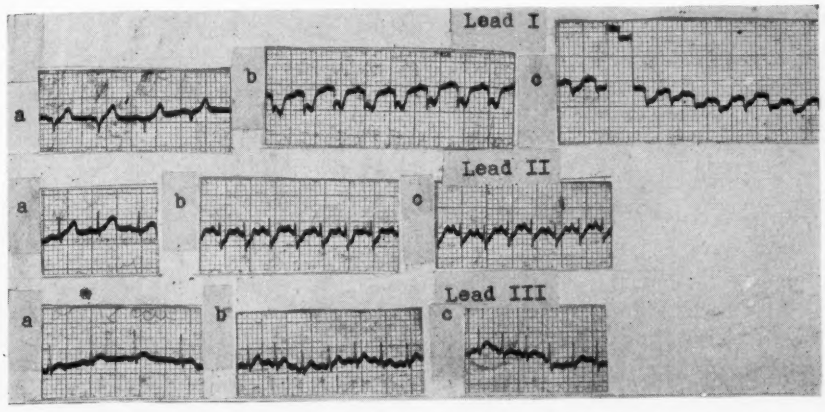


Fig. 7.—Electrocardiogram of Rabbit 30 (male, 2,200 Gm.). *a*, Electrocardiogram taken May 16, 1950, before intravenous injection of histamine diphosphate corresponding to 0.25 mg. histamine base per kilogram; *b*, 3 minutes after injection of histamine (shock reaction took place immediately after the injection); and *c*, 5 minutes after histamine injection.

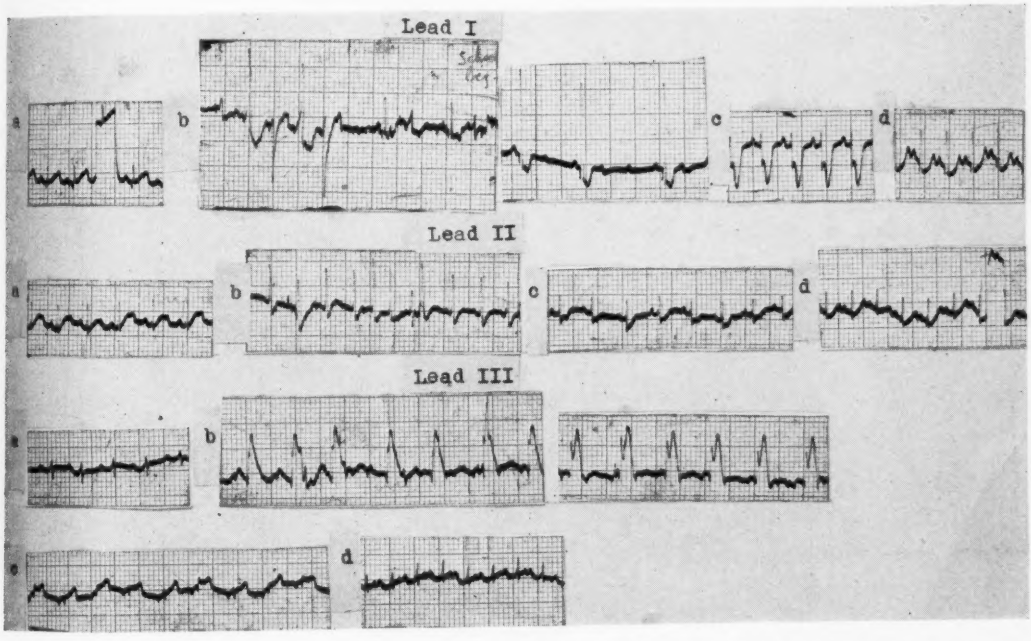


Fig. 8.—Repetition of intravenous histamine injection, 0.45 mg. base total, on Rabbit 30, May, 1950. *a*, Before injection (0.45 mg. base in total); *b*, during 2½ minutes after injection (shortly after injection slight convulsions occurred); *c*, 7 minutes after injection; and *d*, 9 minutes after injection.

Microscopic examination showed no interstitial proliferation of the heart. There was only a subepicardial area with a small focus of lymphoid cellular proliferation and slight cellular infiltration of the media of 2 small coronary branches. There was a small cyst of coccidiosis in the liver.

onstration of the variation of the findings. The variation and irregularity of the ectopic extrasystoles are especially marked in Fig. 3, with the interference with ST_3 changes similar to that seen with coronary insufficiency and infarction in human beings. These findings indicate foci of ectopic excitation in the heart musculature, as well as changes in coronary circulation apparently related to spastic constriction of the smooth muscle of the coronary vessel.

Figs. 2 and 5 demonstrate variation of the pathohistologic tissue changes which are a common finding in most of the rabbits subjected to experimental anaphylaxis.

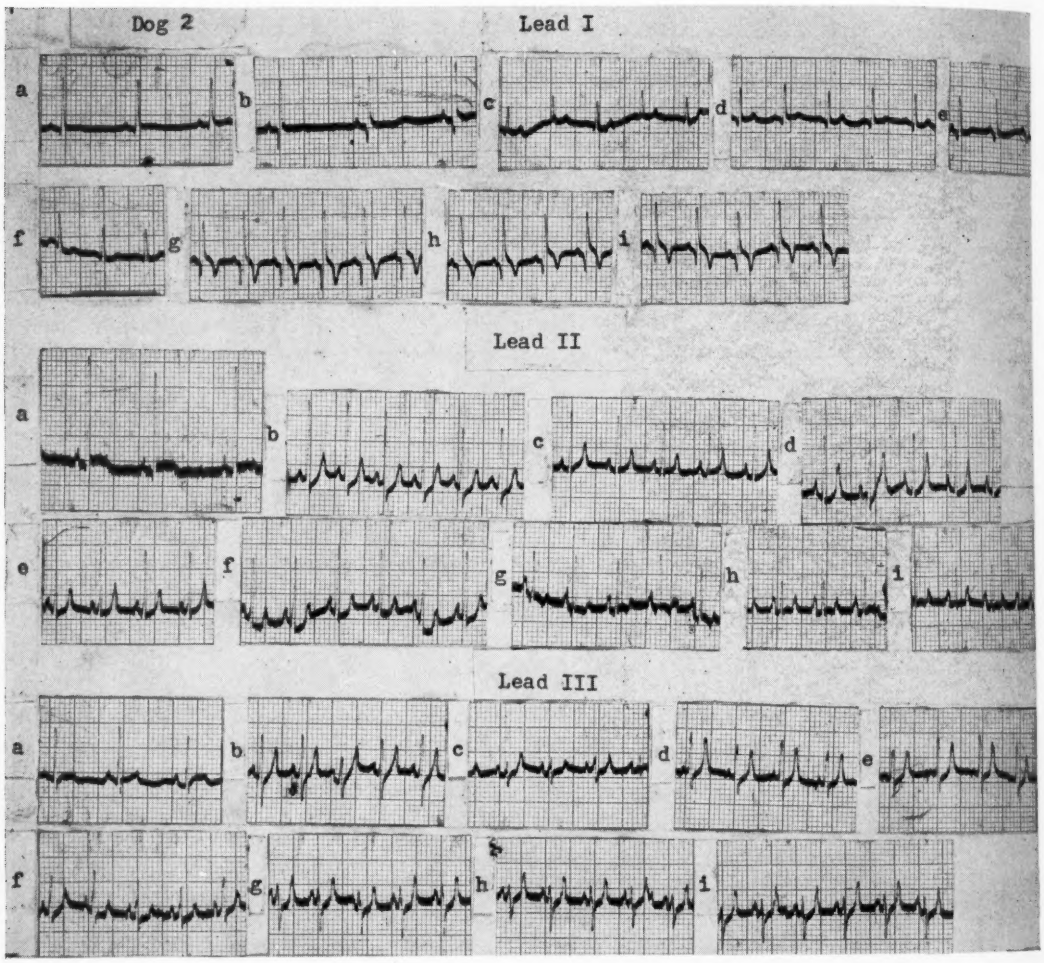


Fig. 9.—Electrocardiogram of Dog 2 (male, 11 kg.) recorded on May 5, 1950. The first horse serum injection, 11 c.c. intravenously, was given April 18, 1950. The second intravenous horse serum injection was given May 5, 1950. *a*, Before horse serum injection; *b*, 0 to 3 minutes after horse serum injection; *c*, 3.30 to 5.45 minutes after injection; *d*, 6 to 7 minutes after injection; *e*, 7.30 to 8.30 minutes after injection; *f*, 10 to 11.30 minutes after injection; *g*, 14 to 15.30 minutes after injection; *h*, 17 to 18 minutes after injection; and *i*, 22 to 24 minutes after injection.

The animal died 32 minutes after the injection of horse serum.

In passive sensitization experiments using 5 rabbits similar but less pronounced electrocardiographic changes were obtained. In these rabbits, passive sensitization was secured with a total injection of 10 to 14 ml. of rabbit serum obtained from sensitized rabbits. No electrocardiographic changes were observed during or after this injection. The anti-horse precipitin titer of the rabbit serum which was used was between 1:5,000 and 1:10,000, tested with the method of serial dilution of antigen. Twenty hours after this passive sensitization injection, horse serum antigen, 10 ml. per kilogram was injected intravenously. The typical short-lasting electrocardiographic changes were seen. These electrocardiographic changes were also present when the anti-horse serum had been exposed for 1 hour to a temperature of 56° C. before it was injected. One hour is the time required for the inactivation of reagins but without significant effects on the precipitin antibodies.

The amount of histamine which is estimated to be released in an anaphylactic reaction in a rabbit is approximately 0.1 to 0.3 mg. per kilogram.[22] Such injection of histamine base, administered intravenously in unanesthetized rabbits, results in very pronounced electrocardiographic changes which show some similarity with those described and demonstrated after antigen injections in sensitized animals. Such histamine injection in Rabbit 30 (Figs. 7 and 8) illustrates these changes with extrasystoles, ST depression in first lead, and monophasic ST in the third lead.

In dogs, similar electrocardiographic pattern changes following antigen injections 17 days after initial sensitization could not be obtained. Three dogs were sensitized, 2 with horse serum (1 ml. per kilogram intravenously) and the third with 1 ml. per kilogram of egg albumin (10 per cent solution). Seventeen days later the second injection of antigen in the same quantities failed to produce electrocardiographic changes similar to those observed in rabbits.

The changes observed were a slight tachycardia with an elevation of the T wave. The negative T_1, appearing usually 15 to 20 minutes after the injection, was seemingly correlated to the increasing circulatory failure preceding the period of premortal changes. All 3 animals succumbed between 25 and 45 minutes after injection. (Fig. 9 shows an electrocardiogram 24 minutes after injection.) This differs from the findings of Robinson and Auer.[21]

DISCUSSION

In an attempt to elucidate the mechanism associated with the anaphylactic reaction, especially its correlation to autonomic reflex mechanisms, it was necessary to search for more reliable biological tests of the antibody-antigen reaction in vivo during the anaphylactic process. General or lethal anaphylactic shock reaction in rabbits is, as mentioned previously, not a frequent event and therefore not a reliable experimental test for studies of anaphylaxis. This applies particularly in the research on the prevention of anaphylaxis with drugs, such as antihistamines and recently ACTH and cortisone (17-hydroxy-11-dehydrocorticosterone), or other therapeutic measures, such as biophysical procedure (x-rays, irradiation, and so on). For example, drugs such as the

antihistamines are routinely evaluated by their protective effect against injection of histamine. Histamine, whatever its role, is certainly not the only factor involved in the anaphylactic reaction of the tissue and especially of the whole organism.

The electrocardiographic changes, which occur almost invariably, could be an aid in the evaluation of therapeutic measures against anaphylaxis as well as an experimental means for the further investigation of the mechanism of the anaphylactic reaction or shock.

In this analysis we do not make a detailed comparison with the results obtained by Auer and Robinson[20] because their observations included only studies with the second lead where their findings correspond to our records of the second lead with the exception of those in vagotomized animals, which will be reported later. The first and third leads are those in which the electrocardiographic pattern changes are most prominently and typically expressed.

We believe that these electrocardiographic pattern changes may be a partial expression of smooth muscle spasms of coronary vessels, additional anoxemia of the heart muscle due to contraction of the arterioles of the lungs, and permeability changes of the tissue.

Apparently, in rabbits the heart represents a shock organ in which the cell injury following antigen-antibody reaction results in the most persistent expression of the anaphylactic process.

It is questionable and problematic if these electrocardiographic patterns represent the acute dynamic expression and initiation of the pathologic tissue changes which follow the antigen-antibody cell reaction. The fact that some animals gave similar reaction after the first sensitizing injection of antigen, presumably in absence of antibodies, indicates that the ability to react in such a way may not be specific. It may be potentially present but does not manifest an effect, as a rule, until the sensitivity threshold is at a proper level.

SUMMARY AND CONCLUSIONS

1. An abnormal electrocardiographic pattern occurring routinely in unanesthetized rabbits during the anaphylactic reaction has been demonstrated.

2. These changes are also obtained with passive sensitization.

3. The significance and possible use of these changes as a biological test in the evaluation of anaphylactic reaction have been discussed.

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ABSENCE OF NONSPECIFIC ANAMNESTIC STIMULATION OF ANTISTREPTOLYSIN IN PNEUMOCOCCUS PNEUMONIA*

CLARENCE Y. SUGIHARA, M.D., AND THEODORE L. SQUIER, M.D., MILWAUKEE, WIS.

WITH THE TECHNICAL ASSISTANCE OF CAROL FEUERPFEIL

DURING studies to determine the frequency and significance of increased titers of antistreptolysin-o in a group of patients with respiratory allergy, transitory increases in titer were noted frequently. This was true both in patients whose symptoms were regarded as of "extrinsic" or atopic origin and in those believed to have symptoms due to infectious causes. In a small group of patients in this latter group, a prolonged elevation in titer of antistreptolysin-o was observed. This increase when maintained for 3 months or more was believed to indicate continued stimulation from recurrent or residual infection with group A hemolytic streptococci. However, because an anamnestic rise in titer of some antibodies is known to occur after nonspecific as well as specific stimulation, it seemed desirable to observe the effect of acute respiratory infections due to organisms other than hemolytic streptococci.

Reported observations of an increased production of antistreptolysin-o due to anamnestic stimulation from heterologous antigens have been inconsistent and inconclusive. One of Coburn and Pauli's[1] rheumatic patients who developed pneumonia failed to show any alteration in antistreptolysin titer. Coburn and Pauli[2] also noted that during an influenza epidemic among their rheumatic fever patients the antistreptolysin titers remained unaltered. Furthermore, they observed that typhoid immunizations in 10 patients convalescing from rheumatic fever did not alter the antistreptolysin level. Lippard and Johnson[3] found an elevated antistreptolysin titer in only 1 of 21 children with miscellaneous infections. Coburn and Pauli[1] reported an increased antistreptolysin titer in 1 of 9 patients with lobar pneumonia. In a more extensive series Longcope[4] observed significantly increased antistreptolysin titers in 16.7 per cent of those patients with chronic disease conditions and in 22.7 per cent of those with infectious diseases. In the latter category, 4 (16.6 per cent) of 24 patients with pneumonia had high titers. Longcope was unable to determine whether the pneumococcus caused the rise in antistreptolysin titer or whether concomitant or earlier streptococcal infection was responsible.

To investigate further the possible anamnestic stimulation of antistreptolysin by unrelated bacterial agents we have studied the antistreptolysin titer of 104 patients with pneumonia.

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*From the Division of Allergy, Milwaukee County Hospital and the Department of Medicine, Marquette University School of Medicine.

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METHOD OF STUDY

The clinical diagnosis of pneumonia was confirmed in most instances by roentgenograms. Sputum cultures, blood cultures, or cultures of both sputum and blood were done on each patient. Pneumococci recovered in cultures were typed whenever possible. The technique employed for titration of antistreptolysin was that described by Rantz and Randall.[5] A titer of 250 units per ml. was regarded as a significant elevation. Whenever possible 2 or more separate determinations were made on each patient. However, with the use of antibiotics, recovery was often so rapid that patients were discharged from the hospital and contact lost before the desired determinations could be made.

RESULTS

A total of 215 antistreptolysin titrations were made on blood from 104 patients with pneumonia. Patients included in the study were divided into 2 groups. One group consisted of 30 patients from whom pneumococci were isolated. Twenty-four of these (80 per cent) had positive blood cultures; 2 had positive spinal fluid cultures, and from 4 patients pneumococci were recovered only from sputum cultures. Elevated antistreptolysin titers (250 units or more) were found in 9 patients (30 per cent) in this group. (Table I.) In 4 of these, the antistreptolysin titer of 250 units remained unchanged in all observations. One of these patients gave a history of scarlet fever and rheumatic fever at the age of 13 years. In 2 patients in this group a dubious rise in titer of one tube only occurred and in 3 patients there was an increase in antistreptolysin indicated by a rise through 2 or more tubes. One of these latter patients had had frequent sore throats and recurring tonsillitis. Observations on one 59-year-old patient (Case 2) who had been admitted previously in May, 1948, with pneumonia seemed especially significant. At that time, 18 days after the onset of pneumonia, there was an elevated antistreptolysin titer of 250 units, but unfortunately the records did not show the bacterial etiology of the pneumonia. She gave a history of scarlet fever at the age of 9 years and rheumatic fever at the age of 25 years. In January, 1949, she again had pneumonia and on this occasion pneumococci were recovered from the blood. Six days following the onset of this attack the antistreptolysin titer was found to be 50 units. Subsequently there was one reading of 125 units, 29 days after the onset of this pneumonia. Otherwise all subsequent antistreptolysin determinations were constant at a level of 50 units. In one patient of the group (Case 30), an observed increase in antistreptolysin titer suggested a possible anamnestic response. A 42-year-old man (Case 30), who had previously had pneumonia in 1912 and in 1943, had been subject to frequent attacks of tonsillitis, the last of which had occurred 4 or 5 months prior to his illness with pneumococcus type I pneumonia. The antistreptolysin level, which was found to be 50 units the first day after onset of the pneumonia, rose to 500 units on the eighth day and to 833 units on the fourteenth day.

The second group comprised 74 patients with pneumonia from whom pneumococci were not recovered. (Table II.) Hemolytic streptococci were isolated from sputum cultures of 29 of these patients and from the blood stream of one additional patient. Unfortunately, no group determinations of the beta-hemoly-

TABLE I. 30 PATIENTS WITH PNEUMONIA FROM WHOM PNEUMOCOCCI WERE RECOVERED

PATIENT	AGE	SEX	BLOOD CULTURE	OTHER CULTURES	ANTI-STREPTOLYSIN-O TITER (ASL)	DATE (1949)	INTERVAL FROM PNEUMONIA ONSET (DAYS)	REMARKS
1. M. S.	20	F	Pneumococci		50	Jan. 11	18	? History rheumatic fever
2. E. F.	59	F	Pneumococci		50	Jan. 6	6	Pneumonia May 11, 1948; ASL 250 May 29, 1948; Scarlet fever at 9 years of age; rheumatic fever at 25 years of age
					50	Jan. 11	11	
					125	Jan. 29	29	
					50	Mar. 15		
					50	Sept. 12		
					50	Nov. 3		
3. H. B.	49	M	Pneumococci		125	Jan. 11	X*	Alcoholic
4. O. B.	64	M	Pneumococci		250	Jan. 27	24	
					250	Feb. 15	43	
					250	Mar. 12	68	Extrarenal uremia
5. J. C.	38	M	Pneumococci		12	Jan. 22	21	
6. C. F.	45	M	Pneumococci (Jan. 29, 1949)		100	Feb. 16	21	
					100	Feb. 26	31	
			Pneumococci (Nov. 16, 1949)		12	Nov. 15	X	
					12	Nov. 28	X + 16	
					12	Nov. 29	X + 17	
7. R. P.	31	M	Pneumococci		50	Feb. 4	8	
8. M. B.	66	F		Spinal fluid pneumococci Type 1	250	Feb. 12	20	Meningitis
					250	Apr. 13	80	
9. J. S.	71	M		Pneumococci in sputum	250	Feb. 21	X	
					250	Mar. 7	X + 14	
10. H. F.	62	M	Pneumococci Type VIII		50	Feb. 26	11	
					100	Mar. 4	17	
11. E. Z.	43	M	Pneumococci Type I		50	Feb. 24	5	Empyema?
					100	Mar. 5	14	
					250	Mar. 12	21	
					250	Apr. 1	41	
12. N. S.	63	M	Pneumococci		100	Mar. 12	X	
					125	Mar. 24	X + 12	
					166	Apr. 7	X + 26	
13. A. R.	64	F	Pneumococci		50	Mar. 25	4	
					125	Apr. 7	17	
					125	Apr. 21	31	
14. M. K.	83	F		Pneumococci in sputum	50	Mar. 25	4	
					125	Apr. 7	17	
					125	Apr. 21	31	Pleural effusion, left
15. F. S.	59	M	Pneumococci Type VIII		12	Mar. 30	18	
					100	Apr. 7	25	
					125	Apr. 21	39	Lung abscess
16. J. G.	55	M	Pneumococci		0	Mar. 26	9	
17. H. S.	42	M	Pneumococci Type II		333	Mar. 30	7	Empyema
					500	Apr. 7	15	
					500	Apr. 21	29	
18. R. F.	77	F	Pneumococci Type III		0	Apr. 1	2	
					50	Apr. 14	15	
					0	Apr. 21	22	
19. S. R.	61	M	Pneumococci Type II		100	Apr. 7	X	

TABLE I—CONT'D

PATIENT	AGE	SEX	BLOOD CULTURE	OTHER CULTURES	ANTI-STREP-TOLY-SIN-O TITER (ASL)	DATE (1949)	INTERVAL FROM PNEU-MONIA ONSET (DAYS)	REMARKS
20. S. M.	42	M	Pneumococci Type I		166	Apr. 7	11	Frequent sore throat
					250	Apr. 14	18	
21. P. S.	63	M	Pneumococci Type II		50	Mar. 14	X	
					100	Apr. 21	X + 38	
					12	May 2	X + 47	
					12	May 12	X + 57	
22. J. B.	70	F		Pneumococci in sputum	125	Apr. 14	14	
					125	Apr. 21	21	
23. C. B.	48	M		Spinal fluid pneumo-cocci	50	Apr. 21	X	Meningitis
					12	May 2	X + 9	
					12	May 13	X + 20	
24. B. B.	74	F	Pneumococci Type III		50	Apr. 28	22	
25. A. G.	41	M	Pneumococci		250	Apr. 20	9	Scarlet and rheumatic fever at age of 13 years
					250	May 5	14	
26. F. C.	68	M	Pneumococci Type II		100	May 16	20	
					250	May 27	31	
					250	Jun. 6	41	
					250	Jun. 13	48	
					125	Jun. 27	62	
					250	Aug. 9	95	Pleural effusion
27. R. K.	41	M	Pneumococci		50	May 17	6	
28. L. P.	70	M		Pneumococci in sputum	50	Jun. 2	X	
29. W. W.	50	M	Pneumococci		12	Jun. 9	15	
					12	Jun. 20	26	
30. I. R.	42	M	Pneumococci Type I		50	Sept. 8	1	Frequent sore throat, last in spring of 1949; pneumonia 1912 and 1943
					500	Sept. 15	8	
					833	Sept. 21	14	
					833	Oct. 10	33	

*X indicates unknown day of onset.

tic streptococci recovered could be made. It is reasonably certain that some of the recovered organisms did not belong to Group A and therefore would not be specifically concerned with any observed rise in antistreptolysin titer. In this second group of 74 patients an elevated antistreptolysin titer was found in 23 (31 per cent). Increased antistreptolysin titers were found in 12 (40 per cent) of the 30 patients from whom hemolytic streptococci were cultured. The one patient (Case 38) who had positive blood culture for hemolytic streptococci was found to have an initial antistreptolysin titer of 50 units; 21 days later the titer had increased to 333 units. In 4 additional patients blood cultures were positive for *Hemophilus influenzae,* for nonhemolytic streptococci, and in 2 patients, for *Staphylococcus albus.* Only one of these patients (Case 59) from whom the blood culture was positive for *H. influenzae* and from whom hemolytic streptococci in addition were isolated from the sputum showed an increased antistreptolysin titer. Among the 44 remaining patients of this group from whom no hemolytic streptococci were recovered, only 10 (22.7 per cent) were found to have increased antistreptolysin levels.

TABLE II. SEVENTY-THREE PATIENTS WITH PNEUMONIA; PNEUMOCOCCI NOT RECOVERED

PATIENT	AGE	SEX	BLOOD CULTURE	OTHER CULTURES	ANTI-STREPTOLYSIN-O TITER (ASL)	DATE (1949)	INTERVAL FROM PNEUMONIA ONSET (DAYS)	REMARKS
31. R. J.	37	M			50	Jan. 11	17	
32. M. S.	69	F			50	Jan. 11	19	
33. E. C.	53	M		Hemolytic streptococci in sputum once	0	Jan. 11	8	
34. P. K.	24	M			12	Jan. 8	4	Occasional sore throat
35. V. C.	26	F		Hemolytic streptococci once	50	Jan. 18	11	
36. A. B.	78	F			0	Jan. 20	15	
					0	Feb. 2	28	
37. I. S.	43	M			0	Jan. 23	X	Bronchiectasis or empyema
					0	Feb. 12	X + 20	
38. A. M.	74	M	Hemolytic streptococci		50	Jan. 22	X	
					333	Feb. 12	X + 21	
39. P. S.	60	M		Hemolytic streptococci	12	Jan. 22	13	
					50	Feb. 12	34	
40. M. M.	67	F			100	Jan. 7	8	
					50	Jan. 27	28	
					50	Feb. 12	44	
41. J. S.	42	M			100	Feb. 11	22	
42. L. S.	69	M		Hemolytic streptococci	250	Feb. 16	32	
43. R. T.	61	M		Hemolytic streptococci	50	Feb. 17	5	Scarlet fever at age of 12 years
44. S. L.	55	M		Hemolytic streptococci	50	Feb. 17	11	
					50	Feb. 26	20	
45. L. M.	75	F		Hemolytic streptococci	333	Feb. 17	X	Frequent childhood sore throats
					625	Feb. 26	X + 9	
					100	Mar. 3	X + 14	
46. L. S.	47	M			50	Feb. 24	13	
47. J. H.	2	M			100	Mar. 5	10	
48. R. L.	3	F			12	Mar. 4	X	
49. F. G.	22	M		Hemolytic streptococci	50	Mar. 4	14	
					50	Mar. 12	22	
50. W. M.	48	M			100	Mar. 4	12	
					100	Mar. 12	20	
51. F. L.		M		Hemolytic streptococci	50	Mar. 8	12	Empyema
					12	Mar. 21	25	
	46				50	Apr. 21	50	
52. W. K.	39	M			0	Mar. 8	6	
53. A. A.	54	M		Hemolytic streptococci	50	Mar. 14	34	
54. O. K.	60	M		Hemolytic streptococci	125	Mar. 12	13	
					125	Mar. 24	25	
					100	May 2	95	
55. F. D.	70	F			0	Mar. 12	11	
56. B. P.	26	F		Hemolytic streptococci	50	Mar. 17	10	
					100	Mar. 25	18	
57. M. F.	22	F		Hemolytic streptococci	12	Mar. 16	6	
					50	Mar. 24	14	
58. F. A.	89	F			12	Mar. 8	X	Died
					12	Mar. 16	X + 8	
59. R. H.	13	M	*Hemophilus influenzae*	Hemolytic streptococci	125	Mar. 20	31	
					250	Mar. 30	41	

TABLE II—CONT'D

PATIENT	AGE	SEX	BLOOD CULTURE	OTHER CULTURES	ANTI-STREP-TOLY-SIN-O TITER (ASL)	DATE (1949)	INTERVAL FROM PNEU-MONIA ONSET (DAYS)	REMARKS
60. R. K.	51	M			50	Mar. 19	X	
61. J. W.	63	M			12	Mar. 23	9	
62. A. H.	62	M			100	Mar. 25	X	Lung abscess
					100	Apr. 7	X + 13	
63. A. S.	63	M			125	Mar. 30	20	
					250	Apr. 7	28	
64. C. G.	55	M			50	Mar. 30	6	Pulmonary infarction with abscess; died
					50	Apr. 7	14	
					50	Apr. 21	28	
65. M. H.	76	F			12	Mar. 26	9	Diphtheria, pneumonia twice
					50	Apr. 7	21	
					100	Apr. 21	35	
66. M. T.	74	F		Hemolytic streptococci	12	Mar. 26	X	Typhoid, diphtheria
					50	Apr. 7	X + 12	
67. F. H.	33	M			125	Apr. 1	X	
68. L. H.	61	M			100	Mar. 26	19	
					250	Apr. 7	21	
69. I. S.	69	F		Hemolytic streptococci	500	Apr. 7	17	
					250	Apr. 21	31	
70. E. L.	73	F			250	Apr. 7	13	Frequent sore throat past winter
71. Z. O.	53	M		Hemolytic streptococci	500	Apr. 7	X	Frequent sore throat; upper respiratory infection for 2 months
72. S. M.	42	M			166	Apr. 7	11	
73. J. S.	73	M			250	Apr. 7	22	
					0	Apr. 21	36	
74. E. M.	38	F		Hemolytic streptococci	100	Apr. 9	3	
75. A. K.	76	M			125	Apr. 14	X	
					50	May 2	X + 18	
					50	May 10	X + 26	
76. S. F.	46	M		Hemolytic streptococci	250	Apr. 14	5	
					125	Apr. 21	12	
					100	May 2	23	
					125	May 10	31	
77. C. T.	37	M		Hemolytic streptococci	50	Apr. 21	9	
					0	May 2	20	
					12	May 12	30	
					12	May 25	43	
78. L. K.	49	M			12	Apr. 21	12	
79. S. G.	45	M		Hemolytic streptococci	250	Apr. 21	29	
80. R. J.	19	M		Hemolytic streptococci	125	Apr. 21	15	
81. C. N.	70	M		Hemolytic streptococci	250	Apr. 21	X	Pleural effusion
					50	May 2	X + 11	
					100	May 10	X + 19	
					250	Jun. 4	X + 44	
					125	Jun. 22	X + 62	
82. A. R.	84	F			100	Apr. 21	18	
					12	May 2	29	
83. C. S.	74	F		Hemolytic streptococci	50	Apr. 30	X	
					50	May 5	X + 5	

TABLE II—CONT'D

PATIENT	AGE	SEX	BLOOD CULTURE	OTHER CULTURES	ANTI-STREPTOLYSIN-O TITER (ASL)	DATE (1949)	INTERVAL FROM PNEUMONIA ONSET (DAYS)	REMARKS
84. L. C.	28	M			12	May 5	9	
					100	May 16	20	
85. L. M.	29	F		Hemolytic streptococci	250	Apr. 11		Pneumonia Oct. 20, 1949, with antistreptolysin 100 units 3 days later; scarlet fever at age of 9, frequent sore throat, bronchiectasis
					125	May 2	5	
					250	May 12	15	
					500	May 31	34	
					333	Jun. 13	47	
					250	Jul. 13	77	
					250	Aug. 17	112	
					50	Nov. 14	201	
86. F. F.	35	M		Hemolytic streptococci	12	May 12	9	
87. F. Gi.	53	M			50	May 12	15	
88. O. W.	63	M			50	May 17	16	Died, pericarditis
89. A. J.	72	M	*Staphylococcus albus*		100	Jun. 6	X	
					100	Jun. 13	X + 7	
90. W. B.	55	M			250	May 25	X	Pleural effusion
91. M. B.	67	M	Nonhemolytic streptococci	Hemolytic streptococci	0	Jun. 13	X	"Rheumatism" years ago
					12	Jun. 20	X + 7	
92. W. R.	69	M			12	Jun. 4	22	
					50	Jun. 13	31	
					50	Jul. 12	60	
93. D. H.	57	M		Hemolytic streptococci	250	Jun. 4	23	
					250	Jun. 13	32	
					125	Jun. 27	46	
94. A. N.	54	M			125	Jun. 8	X	
95. R. O.	27	F			500	Jun. 8	8	Frequent sore throat, tonsillectomy May 12, 1949
96. A. T.	67	M			500	Jun. 16	X	
					166	Jun. 27	X +11	Ill from mid-May
					250	Jul. 12	X + 26	
97. P. B.	58	M			250	Jun. 16	X	
98. F. D.	32	M		Hemolytic streptococci	250	Jun. 16	12	
					100	Jun. 27	23	Pleural effusion
99. J. P.	72	M	*Staphylococcus albus*		0	Jul. 5	X	
100. M. I.	70	M			50	Jul. 5	11	
					50	Jul. 19	29	Penicillin reaction
101. H. D.	57	F			250	Jul. 26	16	
102. W. H.	34	M			100	Jul. 26	4	
					500	Aug. 12	21	Frequent sore throat
103. C. B.	63	M			500	Jul. 26	6	
					250	Aug. 12	23	
104. L. G.	37	F			166	Jul. 1		Lobar penumonia Oct. 16, 1949
					125	Aug. 9		
					50	Oct. 2		
					12	Nov. 1	16	
					12	Nov. 17	22	

DISCUSSION

A majority of earlier reports have indicated that the antistreptolysin titer is affected very little by nonstreptococcal infectious states. Longcope[4] found that 27.7 per cent of 18 patients with chronic rheumatic heart disease had elevated antistreptolysin titers, whereas among another group of patients with chronic diseases but without any stigmata of previous rheumatic disease, 13.6 per cent were found to have increased titers. He noted that in patients having acute hemolytic streptococcal infections the incidence of abnormal titers ranged from 35 to 85 per cent. In contrast to this he found an elevated titer in only 22.7 per cent of those patients who had acute nonstreptococcal infections. Among 24 patients with lobar pneumonia, Longcope reported 4 (16.6 per cent) with increased antistreptolysin titers. In Todd's[6] survey 1 of 9 patients had a high titer; in Lippard and Johnson's[3] series of 11 patients, an elevated titer was found in 1.

In our study of 104 patients with pneumonia, 32 (30.7 per cent) were found to have elevated antistreptolysin titers. In many instances the elevated titer was demonstrated on the first determination. Accordingly, it is impossible to say whether or not the increase in titer was present before the onset of the pneumonia. It is unfortunate that all patients with abnormal titers could not have had repeated determinations. Two or more serial determinations were made, however, from all patients in group I who had pneumococcal pneumonias. Our incidence of elevated antistreptolysin titers of 30.7 per cent is relatively much higher than the 12.7 per cent reported by Rantz and associates[7] for presumably normal individuals. It seems significant that each of our groups of patients with pneumonia included essentially the same percentage with increased antistreptolysin titers; namely, 30.0 per cent of those who had pneumococcal pneumonias, and 31.0 per cent of those in the nonpneumococcal group. This fact lends support to the belief that when increased titers occurred, the cause for increased antistreptolysin probably was attributable to the specific response to the antigen of Group A beta hemolytic streptococci. In another study,[8] we determined antistreptolysin levels in the serums from 160 patients with respiratory allergies. Forty-one (25.6 per cent) of these had significantly elevated titers. In this study 5 (18.5 per cent) patients with uncomplicated atopic rhinitis showed an increase in titer on one or more occasions; 13 (28.8 per cent) of 45 patients with uncomplicated atopic asthma had increased titers; 14 (32.5 per cent) of 43 patients with infectious asthma had elevated antistreptolysin levels. In both of these studies, the large number of patients who were found to have increased antistreptolysin titers suggests that the geographical location may have been a factor leading to the comparatively high incidence. This view is substantiated by the report of Rantz and associates[9] that the antistreptolysin titers of patients residing in the Great Lakes area have a higher mean level than is found for patients from many other parts of the country. Another pertinent observation in relation to the higher levels found in our series is that of Coburn and Pauli,[1] and of Mote and Jones,[10] who reported that hemolytic streptococci were recovered more frequently from indigent patients than from those patients in comfortable economic circumstances. The vast majority of our

patients belonged in the former category. These investigators also considered seasonal influences and found that hemolytic streptococcal infections were more common in winter months, coinciding with the period when pneumonias are prevalent in this locality. The data reviewed confirm our assumption that a relatively greater incidence of elevated antistreptolysin titers in this locale is to be expected. The uniform percentages of increased titers found in the pneumococcal and nonpneumococcal groups of pneumonias indicate that the pneumococcus exerts very little or no anamnestic effect on antistreptolysin production.

SUMMARY

1. Antistreptolysin determinations were made from 104 patients with pneumonias. Elevated levels were found in 32 (30.7 per cent) of these patients.

2. In 30 of these patients pneumococci were isolated. An elevated antistreptolysin level was found in 9 (30.0 per cent).

3. In the remaining group of 74 patients with pneumonias of nonpneumococcal etiology, 23 (31.0 per cent) were found to have an increased antistreptolysin titer.

4. The uniform percentages of elevated antistreptolysin levels found in the pneumococcal and nonpneumococcal groups of pneumonias indicate that pneumococcal infections do not cause a significant anamnestic stimulation to antistreptolysin production.

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ALLERGIC REACTION TO AUREOMYCIN WITH A DEMONSTRATION OF A POSITIVE SKIN TEST TO SERUM CONTAINING AUREOMYCIN*

EARL B. BROWN, M.D., AND MAURICE GOODGOLD, M.D., NEW YORK, N. Y.

IN THE earlier studies of aureomycin,[1-6] the toxic effects of the drug were noted to be diarrhea, nausea, vomiting, and vertigo; no mention was made of allergic reactions. More recently, Peck and Feldman[7] and Parets[8] have reported both rash and angioedema secondary to the use of aureomycin, and with the wider use of the drug more cases of sensitivity may be expected.

The case here reported is of interest because of the association of allergy to aureomycin with allergy to penicillin and light sensitivity, and also the demonstration of a skin reaction to serum containing aureomycin:

R. F., a 52-year-old white woman, had had a history of eczema solare for 15 years. She had been treated by another allergist from 1939 to 1945, and by one of us (E. B. B.) from 1945 to 1949. Prior to the institution of histamine hyposensitization, she was unable to go out in the daylight. All laboratory data, including search for porphyrins, were essentially normal except for a normocytic hypochromic anemia.

In February, 1949, following administration of oral and intramuscular penicillin, she had a severe reaction manifested by a marked flare-up of the light sensitivity, necessitating hospitalization (at another hospital). There she was treated with oral and intravenous antihistaminics, intravenous procaine, saline soaks, and other palliatives to relieve the rash, angioedema, joint pains, and exaggerated eczema solare. Following her discharge from the hospital May 22, 1949, she was advised to take 50 mg. of Benadryl 3 times a day. Histamine injections were started and after January, 1950, she was able to expose herself to sunlight.

In March, 1950, she developed acute sinusitis and bronchitis. Because of persistent hyperpyrexia and her history of previous reaction to penicillin, she was given aureomycin, 500 mg. every 6 hours. Forty-eight hours after the beginning of therapy she became nauseated and the medication was discontinued. Approximately 6 hours after the aureomycin was stopped, she noted severe anal and vaginal pruritus. She was then seen at the gynecologic clinic of another hospital, where wet dressings were prescribed. The following day, she was seen by one of us (E. B. B.) for the first time in a year. At that time, marked rawness and excoriations due to scratching were noted in the genital groove. The anal folds and the labia majora and minora were markedly edematous. The opposing surfaces of the thighs were edematous and erythematous, and the entire area was covered with a diffuse maculopapular eruption. There was also evidence here of secondary trauma due to scratching. The legs, arms, and hands, where exposed to the sun, were covered with a similar rash. The eyelids and nose were slightly edematous. She stated that since she had first noted the eruption her sensitivity to light had become marked again.

Therapy with various ointments and antihistaminics was of little value. On March 30, 1950, she was sent to a dermatologist for roentgen-ray therapy of the genital area. The edema and rash in the groin cleared after 4 weeks and gradually the symptoms of light sensitivity abated. She was instructed to apply 15 per cent para-aminobenzoic acid[9] in lanolin over the exposed areas of her body. Hyposensitization with histamine and monilia was introduced. At present, the patient is asymptomatic.

*From The Institute of Allergy, Roosevelt Hospital.

As can be seen by referring to Fig. 1, the patient displayed a delayed reaction to the aureomycin and within 24 hours a marked flare-up of all symptoms was noted. Because of the marked discomfort of the patient and for fear of precipitating a general reaction in a highly emotional individual, a repetition on the intracutaneous test was not done at this time.

The control was a nonallergic individual who had had no previous aureomycin therapy.

	Patch test with aureomycin Powder	Scratch test aureomycin in saline solution (100 mg/ml)	Intracutaneous test with 0.05 ml aureomycin, 100 mg/ml	
			Immediate	Delayed (24 hour)
Patient	negative	negative		
Control 1	negative	negative		negative

Fig. 1.—Results of patch and intracutaneous tests with aureomycin.

	April 4, 1950		June 16, 1950	
	Aureomycin serum (1)	Control	Aureomycin serum (1)	Control
Patient				
Control 1	not done	not done		
Control 2	not done	not done		

Fig. 2.—Reactions to intracutaneous tests with Serum 1 containing aureomycin and normal serum.

Passive transfer testing was done according to the method of Prausnitz and Kustner.[10] Five hundredths millimeter of the patient's serum was injected intracutaneously on the arm of a nonallergic person. Forty-eight hours later, 0.05 ml. of a solution of aureomycin containing 100 mg. per milliliter was injected intracutaneously at the site of the previous injection. No reaction was elicited.

It was felt that a drug protein conjugate such as described by Leftwich[11] for the sulfonamides and Gelfand[12] for Mercuhydrin might be formed in the body by aureomycin. Blood was withdrawn from a patient who had received aureomycin, 250 mg., every 6 hours for a period of one week. The serum was separated from the whole blood and passed through a Seitz filter. Sterility tests were negative after one week. At this time, 0.1 ml. of a normal control

serum, as well as 0.1 ml. of this serum, was injected intracutaneously into the patient. The results can be found in Fig. 2. The patient and 2 controls were tested with the same samples of sera 10 weeks later.

The patient was tested with mold extracts as shown in Fig. 3. It was felt that there might be a relation between sensitivity to these organisms and the reactions to penicillin and aureomycin.

Hyposensitization with *Monilia albicans* was attempted, but the highest dosage we were able to achieve was 80 PNU. Above this dosage, she had a severe local reaction which lasted for 48 hours.

Mold Extracts	Reaction
Althernaria(1,000 PNU)	o
Aspergillus (1,000 PNU)	o
Cephalothecium(1,000 PNU)	o
Cladosporium(1,000 PNU)	o
Hormodendron(1,000 PNU)	o
Monilia albicans(1,000 PNU)	
Oidiomycin(1-100)	o

Fig. 3.—Results of intracutaneous tests with mold extracts.

	Aureomycin serum(2)	Control serum
Patient		o
Control 1	o	o
Control 2	o	o
E.B.B.		o

Fig. 4.—Reactions to intracutaneous tests with Serum 2 containing aureomycin.

In view of the unusual reaction as seen in Fig. 2, it was felt that further testing with another aureomycin serum was indicated. Accordingly, blood was withdrawn from another patient who had been on aureomycin, 500 mg., every 6 hours for 7 days. This patient had had no evidence of any toxicity to the drug. The serum was separated and tested intracutaneously as previously described. As shown in Fig. 4 the patient and two controls displayed reactions similar to those noted in Fig. 2; the patient showed a marked reaction, while the controls showed little or no reaction.

While the investigative study was going on, one of us (E. B. B.) had used aureomycin ointment locally for a follicular conjunctivitis. This salve had been applied over a period of 2 months. At the end of that time, periorbital dermatitis was noted which cleared with the use of wet boric acid dressings and avoidance of the salve. The results of a skin test with the aureomycin serum No. 2 on E. B. B. are also seen in Fig. 4.

COMMENT

Parets[8] reported a case similar to ours in which a severe penicillin reaction antedated by one year the administration of aureomycin. Peck and Feldman[7] did not mention whether their patients suffering from reactions to aureomycin had received penicillin, although 2 of their cases received sulfonamides without ill effect. The nature of the coexistence of these 2 reactions remains undetermined at present.

The relationship of the light sensitivity to the penicillin and aureomycin reactions is interesting. Canizares[13] thought that penicillin might be a photosensitizing agent. However, since his patient had previously had one of the sulfonamides, which are known to be photosensitizing agents, doubt must be thrown on his evidence.[14]

The marked exacerbation of the symptoms following the intracutaneous test with aureomycin solution was strongly suggestive evidence that the patient's skin eruption was an allergic reaction following the oral use of aureomycin. The positive skin reaction to the serum containing aureomycin is of greater significance. The marked sensitivity to the aureomycin-containing serum following a negative test 2 months previously was of some interest. Certainly, refrigeration of the serum for 2 months could not be held responsible for the marked reaction, since the control serum was kept under the same conditions for the same period of time. It is also to be expected that both sera would have given similar responses on the 2 controls.

The repetition of the skin test with the second aureomycin-containing sera on both the patient and the 2 same controls which had been previously used is additional evidence for the existence of a drug conjugate. The positive skin test on the second patient who also had an aureomycin reaction gives further credence to the presence of an aureomycin-protein conjugate in the serum.

Aureomycin serum is now readily available. In allergic individuals who have shown marked reactions to penicillin or other antibiotics aureomycin should not be administered until the skin test with serum containing aureomycin has been performed.

The positive skin test to *Monilia albicans* cannot be considered as significant, as it is fairly common; however, the fact that we were not able to raise the dosage above 80 PNU we believe indicated a marked sensitivity of the patient. It is felt by some observers[15] that the perianal rash following the use of aureomycin is caused by *Monilia albicans*. The antibiotic is presumed to destroy microorganisms which previously had inhibited the growth of *Monilia*

albicans in those patients susceptible to it. The fact that the reaction in this case was so severe might well be related to this patient's marked sensitivity to *Monilia albicans.*

SUMMARY

A case of angioedema and rash due to the ingestion of aureomycin is presented. This case is of interest because of the relationship between the exacerbation of eczema solare and the aureomycin reaction preceding it. A delayed positive skin test to aureomycin solution and an immediate reaction to serum containing aureomycin were demonstrated.

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Editorial

ALLERGIC DISEASES IN THE ARMED FORCES

With draft boards again calling up young men for service in the armed forces, the physical standards for induction are of interest to all civilian physicians. Many allergists are acting as advisers to draft boards, while others are consulted by their patients as to their probable eligibility and are writing letters about their patients which are important in enabling the draft boards to determine physical acceptability. In either case fair and helpful advice requires some knowledge of the standards which have been established with the advice and cooperation of the National Research Council and which are now uniform for the Army, Navy, and Air Force. Inquiry among even those allergists working with draft boards has revealed a disturbing number who are not familiar with these standards.

The importance of proper consideration of allergic diseases, particularly asthma, in the selection of inductees is apparent to all physicians who served in the armed forces during World War II or who have since been associated with hospitals or clinics of the Veterans Administration. The American Academy of Allergy has appointed a Committee on Standards for Induction of Draftees into the Armed Forces to study this problem. The report of this committee, which is published in this issue, gives some indication of the problem which asthma has presented to the various armed services.

The statistics also show that more than one-half of these cases of asthma existed prior to induction, and therefore were recognizable risks that need not have been accepted by the government. While every citizen realizes that dire military emergency may require the services of all who can be even temporarily useful, the present limited mobilization does not justify the induction of those whose physical condition makes likely a serious impairment of health by service and causes expense to the government out of proportion to the service rendered by the individual.

The physical standards applicable to allergic disease given in detail in the committee report are relatively simple. Mild hay fever, acute eczema, and urticaria are acceptable, while severe hay fever, asthma during adult life and severe allergic dermatoses are not acceptable. The justice of these standards is apparent to all who are familiar with the situation. Hay fever, except in unusually severe cases, has not proved a cause of serious disability, while asthma which has been relatively mild during civilian life is exceedingly prone to cause serious disability in active service which necessarily entails unusual exposure to cold, wet, and dusty conditions. If waste of effort and unnecessary disruption of lives is to be avoided, these standards must be applied at the draft board level.

The allergist can render valuable aid both to the individual and the government by exercising careful judgment in these matters when acting as an ad-

viser to a draft board. Due to the periodic nature of most allergic diseases, decisions must often be based largely on reports from the prospective draftee's physician, whose duty is to furnish unbiased and factual information. While the opinion of the private physician as to the acceptability of his patient is not expected, knowledge of the standards will guide him in supplying the type of information needed. Since the standards are based on specific disease manifestations rather than the allergic state, the statement that a patient was seen on certain dates with objective physical signs of asthma is more valuable than a long series of skin tests performed during a period of freedom from symptoms. If hay fever has caused actual serious disability during civilian life, factual evidence is essential.

As physicians and citizens we bear a responsibility both to the individual and to the government in aiding in the fair and wise application of the standards that have been established.

W. B. S.

Announcements

Postgraduate Course in Allergy

A postgraduate course in allergy will be offered by the American Academy of Allergy on June 14, 15, and 16 in Montreal, Canada. It will be sponsored by the Faculty of Medicine of McGill University, and will be held at the Royal Victoria Hospital in Montreal.

Any interested physician in the United States or Canada may attend. The fee for the course is $40. Applications should be sent to Bram Rose, M.D., Royal Victoria Hospital, Montreal 2, Canada.

Program

Thursday, June 14, 1951

9:00–10:00 A.M.: Fundamental Concepts of Immunity; Antigen-Antibody Relationships, E. A. Kabat, M.D., Columbia University.

10:00–11:00 A.M.: Applied Immunology in Allergic Disorders, W. B. Sherman, M.D., Columbia University.

11:00–12:00 A.M.: Physiology of Allergic Mechanisms; Role of Histamine, Bram Rose, M.D., McGill University.

2:00– 3:00 P.M.: The Pituitary-Adrenal Relationships, J. S. L. Browne, M.D., McGill University.

3:00– 4:00 P.M.: ACTH and Cortisone in Relation to Allergic Mechanisms, Bram Rose, M.D., McGill University.

4:00– 5:00 P.M.: Oto-Rhinology in Relation to Allergy, W. J. McNally, M.D., McGill University.

Friday, June 15, 1951

9:00–10:00 A.M.: Patho-Physiology of Allergy; Respiratory Function Tests, P. Pare, M.D., K. K. Pump, M.D., and Bram Rose, M.D.

10:00–11:00 A.M.: Differential Diagnosis of Asthma, C. H. A. Walton, M.D., University of Manitoba.

11:00–12:00 A.M.: Collagen Disease, Lyman Duff, M.D., McGill University.

2:00– 3:00 P.M.: Allergic Dermatoses, To be announced.

3:00– 4:00 P.M.: Allergy in Children, H. L. Bacal, M.D., McGill University.

4:00– 5:00 P.M.: Therapeutics—Antihistamines, Modified Adrenalins, H. L. Mitchell, M.D., McGill University.

7:00 P.M.: Dinner, followed by Round-Table Discussion.

Saturday, June 16, 1951

9:00–10:00 A.M.: Psychiatric Aspects of Allergy, Eric Wittkower, M.D., McGill University.

10:00–11:00 A.M.: Hay Fever, J. D. L. Fitzgerald, M.D., University of Toronto.

11:00–12:00 A.M.: The General Adaptation Syndrome, Hans Selye, M.D., University of Montreal.

1:00 P.M.: Luncheon.

Session in Allergy at the Meeting of the American Medical Association

A session in Allergy will be included in the program in the section of Miscellaneous Topics at the Meeting of the American Medical Association in Atlantic City, N. J. This session will be held the afternoon of June 13, 1951, with Dr. Samuel M. Feinberg as Chairman and Dr. William B. Sherman as Secretary. The program will include:

Antihistaminics in Allergic Disorder, John H. Mitchell, M.D., Columbus, Ohio. Discussion to be opened by Carl E. Arbesman, M.D., Buffalo, N. Y.

Pollen Prevalence and Pollen-free Areas, Oren C. Durham, Chicago, Ill. Discussion to be opened by Lawrence J. Halpin, M.D., Cedar Rapids, Iowa.

Diagnostic Methods in Food Allergy, Karl D. Figley, M.D., Toledo, Ohio. Discussion to be opened by Mary H. Loveless, M.D., New York, N. Y.

Allergy Therapy. Some Common Misconceptions. (Chairman's Address).
Samuel M. Feinberg, M.D., Chicago, Ill. Discussion to be opened by Horace S. Baldwin, M.D., New York, N. Y.

ACTH and Cortisone in Allergic Diseases (Round Table Discussion).
Robert A. Cooke, M.D., New York, N. Y.,
Marion B. Sulzberger, M.D., New York, N. Y.,
Bram Rose, M.D., Montreal, Canada.

American Academy of Allergy

HISTORIAN'S REPORT

THE Seventh Annual Meeting of The American Academy of Allergy was held at the Statler Hotel in New York City Monday through Wednesday, Feb. 5 to 7, 1951, under the Presidency of Dr. Theodore L. Squier. Dr. Horace S. Baldwin and his Committee on Local Arrangements had everything well planned and under perfect control, except for one major item, namely the nation's railroads.

In spite of the travel handicaps of a nationwide railroad strike, however, the first scientific session on Monday opened at 9:15 A.M. with an attendance of 150. This number had doubled by intermission time. At the succeeding sessions on Tuesday and Wednesday, the assembly room was filled to capacity, often with many standing.

The official registered attendance for the Annual Meeting was 614 members and guests. In addition, 100 wives were registered. Twenty-two members and guests registered from outside the United States, including one each from Argentina, Australia, Finland, Israel, Puerto Rico, British Columbia, New Brunswick, and Nova Scotia; 2 each from Toronto, Canada, Cuba, and Iran, and 8 from Montreal.

Nine highly instructive scientific exhibits were arranged for study. Oren C. Durham, Chairman of the Pollen Survey and the Herbarium Committees, presented the work of these two committees, including the 1950 report for the annual pollen surveys which have been of such value to the Academy for many years.

Thirty commercial exhibitors set up exceptionally attractive booths, in spite of the difficulties of transportation. Recent developments were stressed, and the members and guests showed their appreciation by a constant and heavy attendance at the booths.

The numerous standing and special committees of the Academy held meetings on Friday and Saturday and reported to the Executive Committee at its session on Sunday, February 4. Among the many matters considered by the Executive Committee and subsequently reported to business session of Fellows of the Academy, a few can be mentioned here.

Dr. Piness, Chairman of the Committee on an Independent Board of Allergy, reported that his committee had met earlier in the year with the Advisory Board for Medical Specialties and had again presented their case. Although no action was taken by the Advisory Board, both the American Academy of Allergy and the American College of Allergists have been requested to make nominations to fill vacancies on the Advisory Committee for Allergy to the Boards of Internal Medicine and Pediatrics. Unfortunately the next meeting of the Advisory Board for Medical Specialties was scheduled for February 10, so no report could be made bringing the matter up to current date. Dr. Piness and his committee have been invited by the Advisory Board to attend their meeting on February 10.

Dr. Karl Figley, Chairman of the Military Advisory Committee, reported that his committee had secured data regarding allergy in connection with enlistment and the draft. It appears that definite regulations on various allergic conditions have been issued and are still in force. Among these is one excluding from service those individuals who have had asthma subsequent to the age of 12 years. Through ignorance, or for other reasons, these regulations are not being observed. The Government is still paying pensions, because of disability due to asthma, to over 36,000 men, the equivalent of 2 Army divisions. The Executive Committee voted to send a letter to the appropriate national authorities, calling this matter to their attention.

Some time ago the name and the remaining funds of the Allergy Foundation were offered to the Academy and were accepted. The Executive Committee has considered this matter in detail and presented its action for the approval of the Fellows at the business meeting. The name was changed to "The Foundation for Allergic Diseases." This Foundation is essentially a fund-raising organization, empowered to solicit and receive money for the promotion of research and educational work in allergy. It is an independent body, controlled by a Board of Trustees composed of 12 physicians and 9 laymen. The Academy is linked with the Foundation in that the following officers and committeemen of the Academy are ex-officio members of the Board of Trustees: President, Vice-President, Treasurer, General Chairman of the Committee on Education, Chairman and Secretary of the Research Council.

The annual business meeting of the Fellows of the Academy was held on Tuesday afternoon, February 6.

The retiring President, Dr. Squier, read the Presidential Address, which was of unusual value because of the thoughtfulness of his remarks and the applicableness of his ideas to the problems facing the Academy.

The group received a pleasant surprise when Dr. Squier introduced Dr. Will C. Spain. Dr. Spain gave a brief speech outlining the influence of Dr. Robert A. Cooke in the field of allergy. He traced this influence from Dr. Cooke's initiation, in 1922-1923, of the Society for the Study of Asthma and Allied Diseases, one of the parent bodies of the Academy, through nearly 30 years, during which the field of allergy has developed in the United States. He emphasized the fact that Dr. Cooke had made his many contributions by working with and through others, and by encouraging and stimulating others in their activities. Dr. Cooke was then presented with the scroll of Honorary Fellowship.

In his response, Dr. Cooke spoke on the meaning and worth of tradition in general, and in the Academy in particular, and drew attention to the fact that tradition is not static, but is something to build and to build upon.

The scientific sessions were held on the morning and afternoon of February 5 and 6 and on the morning of February 7.

The guest speakers were William F. Hamilton, Ph.D., Professor of Physiology, University of Georgia School of Medicine, who spoke on The Physiology of the Pulmonary Circulation; David Pressman, Ph.D., Head of

the Section of Immunochemistry, Sloan-Kettering Institute for Cancer Research, who spoke on The Zone of Localization of Antitissue Antibodies; and A. McGehee Harvey, M.D., Professor of Medicine, Johns Hopkins School of Medicine, who spoke on Observations on the Use of ACTH and Cortisone in Allergic Diseases.

Twenty-six papers were read on many subjects related to allergy, which will appear in THE JOURNAL OF ALLERGY. Two excellent colored movies, prepared by Armour & Co., were shown through their courtesy: Physiological Basis for the Action of ACTH in Human Beings, and Therapeutic Use of ACTH in Human Disease.

Socially, the reception given Sunday afternoon, February 4, by the New York Allergy Society, arranged by Dr. James H. Barnard, was very successful indeed, with an attendance of over 200 members and their wives.

The President's Dinner on Monday night was an innovation for the annual meeting. Many of the past presidents of the Academy and of the 2 parent organizations attended, with a number of guests. The speakers were Dr. Robert A. Cooke, for the Association for the Study of Asthma and Allied Conditions, and Dr. Harry S. Bernton, for the American Association for the Study of Allergy. Several others spoke briefly; President Squier presided.

A luncheon was held Tuesday noon for members and guests from outside the United States, at which President Squier, President-elect Baldwin, and Dr. José M. Quintero of Cuba spoke briefly.

The Hostess Committee, of which Mrs. Theodore L. Squier was Hon. Chairman, Mrs. Bret Ratner, Chairman, and Mrs. Horace S. Baldwin, Cochairman, served tea each afternoon. They also arranged various sight-seeing and shopping trips, among them a trip to the United Nations, a fashion show at Jay Thorpe, and trips to Good Housekeeping Institute. The indefatigable work of Mrs. Ratner, Mrs. Baldwin, and their committee made the visit to New York one to be remembered by the "ladies of the Academy."

At the business session the following officers were elected for 1951: President, Horace S. Baldwin; Vice-President, Walter S. Burrage; Secretary, Ben Z. Rappaport; Treasurer, Stanley F. Hampton; Historian, Howard Osgood; Member of Executive Committee, Frank Perlman.

Before closing this report, your historian must mention the indispensable contribution to the unusual success of the meeting made by Mr. James O. Kelley, Executive Secretary of the Academy, who was responsible for the over-all planning and for securing the commercial exhibits, and by Mr. A. H. Luthmers, Assistant Executive Secretary, who saw to the innumerable details. Their work and that of their staff in Milwaukee began months before the meeting date.

The next annual meeting of the American Academy of Allergy will be held in Chicago, Ill., at the Hotel Sherman, on Feb. 18, 19, and 20, 1952.

Following is a list of those elected to the several classes of membership in the Academy on Feb. 6, 1951.

HOWARD OSGOOD, M.D.,
Historian.

American Academy of Allergy

ADVANCED TO FELLOWSHIP, 1951

Johnny A. Blue, M.D.
Earl B. Brown, M.D.
Samuel C. Bukantz, M.D.
Leoni N. Claman, M.D.
Seymour B. Crepea, M.D.
Herbert S. Dieckman, M.D.
Norman J. Ehrlich, M.D.
Charles M. Jenkins, M.D.
Maurice Kaufmann, M.D.
Harry Leibowitz, M.D.
Erving L. Rogers, M.D.
L. E. Seyler, M.D.
S. W. Simon, M.D.
A. M. Targow, M.D.
Louis R. Weiss, M.D.

DIRECT ELECTION TO FELLOWSHIP, 1951

Mario S. Mallen, M.D.
Guido Ruiz-Moreno, M.D.
David A. Williams, M.D.

ELECTED TO HONORARY FELLOWSHIP, 1951

John Freeman, M.D.
Cesare Frugoni, M.D.
C. Prausnitz Giles, M.D.
Carlos Jimenez-Diaz, M.D.

ELECTED TO AFFILIATE MEMBERSHIP, 1951

Leon Rodescu, M.D.

EMERITUS MEMBERSHIP, 1951

Milton B. Cole, M.D.
L. W. Gorham, M.D.

ELECTED TO MEMBERSHIP, 1951

Alois E. Bachman, M.D.
Roslyn Barbash, M.D.
Samuel F. Bassett, M.D.
Irving Berlin, M.D.
Luis E. Betetta, M.D.
A. J. Brennan, M.D.
Max Braitman, M.D.
E. A. Canterbury, M.D.
Gustavo Castaneda, M.D.
Cecil Collins-Williams, M.D.
Claude A. Frazier, M.D.
Stanley S. Freedman, M.D.
William H. Gardner, M.D.
William C. Gauntt, M.D.
Israel Glazer, M.D.
William C. Grater, M.D.
Helen C. Hayden, M.D.
Irving H. Itkin, M.D.
G. Thomas Johnston, M.D.
Solomon D. Klotz, M.D.
Frederick O. Kuehl, M.D.
Henry Kuperman, M.D.
Juan F. Lamas y Parra, M.D.
Harry Lazar, M.D.
William H. Lipman, M.D.
A. Oliveira Lima, M.D.
Connolly J. Malloy, M.D.
A. Matheson, M.D.
Lloyd D. Mayer, M.D.
Murray L. Maurer, M.D.
Oscar E. Lozano Menchaca, M.D.
B. Thomas McMahon, M.D.
James McManus, M.D.
George A. Moll, M.D.
John E. Newland, M.D.
Joseph Noah, M.D.
George A. Peck, M.D.
Jose Joaquin Pedrera, M.D.
Dallas Pond, M.D.
Howard Reed, M.D.
Arnold Dankner, M.D.
Thurman Dannenberg, M.D.
Julius de los Santos, M.D.
H. W. Diefendorf, M.D.
Galen S. Egbert, M.D.
Donald T. Faulkner, M.D.
B. T. Fein, M.D.
Alan R. Feinberg, M.D.
Theodore M. Feinblatt, M.D.
Harold Fisher, M.D.
W. K. Riley, M.D.
Edward H. Roston, M.D.
William Sapsin, M.D.
Ernest J. Saslow, M.D.
Maurice R. Schlanger, M.D.
E. Oskar Schreiber, M.D.

Samuel Schwartzberg, M.D.
Maurice S. Segal, M.D.
Joseph H. Shaffer, M.D.
John L. Shirey, M.D.
Selig A. Shevin, M.D.
Umberto Serafini, M.D.
Miguel A. Solari, M.D.
Charles G. Speicher, M.D.
Robert S. Steel, M.D.
Clarence Y. Sugihara, M.D.
Albert H. Unger, M.D.
Keith E. Weller, M.D.
John B. Welsh, M.D.
Aubrey L. Whittemore, Jr., M.D.

A REPORT OF THE COMMITTEE ON STANDARDS FOR INDUCTION OF DRAFTEES INTO THE ARMED FORCES

THE American Academy of Allergy offered its services to the surgeon generals of the armed forces and the United States Public Health Service for the purpose of defining standards of acceptability of inductees with allergic disorders. The offer was accepted by all services and a committee was appointed to study the question and report.

In accepting this offer, it was pointed out by representatives of the Navy and the Air Force that these services had accepted standards adopted by the Army as laid down in Army Regulations Number 40-115, dated Aug. 20, 1948. These regulations define specifications for acceptance and nonacceptance of draftees. In the category of acceptance 3 "profiles" are defined, depending on the candidate's ability for sustained effort. These regulations were based on a study by a Committee on Medical Sciences of the National Research Council with the assistance of its various subcommittees.

In so far as allergic diseases are concerned, the regulations read as follows:

Hay Fever.—Acceptable if mild, nonacceptable if severe.

Skin Diseases.—Acute eczema acceptable if mild; allergic dermatoses nonacceptable if severe; neurodermatitis, hives, angioneurotic edema, and dermatographism acceptable if not incapacitating during civil life.

Asthma.—Nonacceptable if present to any degree, or if subject has a history of asthma. Acceptable only if history of childhood asthma is accompanied by a trustworthy history of freedom from symptoms since the twelfth birthday.

The committee feels that although the stated allergic disorders may have been better classified and more inclusive, it is in entire accord with the provisions of the regulations. The importance of enforcing these at the draft board level is emphasized by statistics. These indicate that bronchial asthma is far more important in terms of disability than any other allergic manifestation. Allergic dermatoses rank second, but far below asthma. Severe hay fever and other expressions of hypersensitiveness have not been prominent in the over-all picture. To be sure, any allergic individual may develop various symptoms of his underlying disorder, but if some 10 per cent of the younger population is composed of such people, it becomes important to find a focus in order to formulate a practical approach. The committee feels if asthmatic individuals are excluded from the armed services the problem of allergy would be of no great importance.

In World War I, 7,797 patients with asthma (about 2 per thousand) were admitted to army hospitals.[1] This is almost 3 times the number entered for peptic ulcer. Over 30 years later 3,318 veterans of that war whose asthma was service connected (all services) were on the compensation rolls, and 4,806 others became totally incapacitated from the disease in the interim and received pensions. Patients rarely die from asthma and, with new cases appearing, the above

figures represent more than 12 per thousand. As of June 30, 1950, 36,541 veterans of World War II were on compensation rolls and 143 on pensions from the Veterans Administration for asthma.[2]

Table I represents patients with asthma hospitalized by the Navy in World War II. Although the incidence is not high, the percentage of those who had asthma prior to entering the service is high. Had present regulations been in effect, most of them doubtless could have been rejected at the time of induction. The percentage of invalidings emphasizes still further the need of excluding asthmatic individuals from the armed forces. The following passage is taken from the report of the Surgeon General of the Navy in 1945[3]: "In 1944 and 1945, asthma was the most important diagnosis in the class of respiratory diseases in that it had the highest incidence. In 1945, 41 percent were considered to have existed prior to entry in the service; it accumulated 43 percent of all

TABLE I

YEAR	TOTAL STRENGTH, NAVY & MARINE (DEC. 31)	CASES OF ASTHMA (DEC. 31)	EXISTED PRIOR TO ENTERING SERVICE		INVALIDINGS FROM SERVICE		SICK DAYS	SICK DAYS PER CASE
			NO.	PER CENT	NO.	PER CENT		
1941		394	151	38	123	31	17,089	43.4
1942	1,434,146	1424	774	54	449	32	52,687	36.9
1943	2,108,379 (average)	3904	2563	64	1765	45	208,551	53.4
1944	3,674,135	6932	4248	61	3117	45	470,090	67.8
1945	2,717,939	6720	2764	41	5603	83	487,901	72.6
1946	686,701	1403	420	30	898	64	76,915	54.6

sick days for the entire group and 5,603 invalidings during that period. It was seventh in rank among the leading diseases causing attrition by medical discharges." Again, in 1947, the Surgeon General's report states: "Asthma was the cause of 254 invalidings or approximately 60 percent of the 425 cases invalided for the entire class of respiratory diseases. Each new case of asthma averaged 48 days on the sick list. The highest incidence among single causes was for acute pneumonitis and asthma, each detected 597 times."

These examples should suffice without further information in terms of cost, utilization of hospital space, effort of invalidating, and effect on the patient. The problem would be largely resolved if the induction boards were well informed about it and would take proper precautions. This may be the case, and it is hoped that known instances in which frank asthmatic individuals have recently been accepted are exceptions to the rule.

Signed: *Harry L. Alexander, M.D.*
Karl D. Figley, M.D.
Stanley F. Hampton, M.D.

REFERENCES

1. The Medical Department of the United States Army in the World War, Washington, D. C., 1925, Vol. 15, Statistics, Part 2, Government Printing Office.
2. Medical Statistics Division, Veterans Administration.
3. Medical Statistics, United States Navy, 1945, Report of the Surgeon General.

In Memoriam

CARLISS MALONE STROUD

CARLISS Malone Stroud was born in Simpson County, Mississippi, on Aug. 26, 1903. He graduated from the University of Mississippi in 1924 with the degree of Bachelor of Science, and he received his medical degree in 1926 from the School of Medicine, Washington University, St. Louis, Mo. He served his interneship at Barnes Hospital. During this term of service he volunteered to work in the Allergy Clinic of the Washington University Clinics. His volunteer status was made permanent upon its termination and he became a dependable, zealous, and inspiring member of the Clinic. He entered the private practice of medicine in 1928.

He soon perceived that a knowledge of allergy gave one insight into the causes of some clinical syndromes and furnished one with a helpful therapeutic modality. He became a discerning internist who applied the techniques of allergy in appropriate and selected clinical situations. He was particularly intrigued with the dermatologic manifestations of allergy, but he never lost sight of their interrelationship with the basic divisions of medicine and with other allergic manifestations. He firmly believed that a good allergist should never be an unqualified or inept internist.

His energy was seemingly inexhaustible. He had a wide interest in medicine, as shown by membership in the Saint Louis Diabetic Society, in the National Gastroenterological Society, in the American Therapeutic Society, in the American Association for the Advancement of the History of Medicine, in the American Academy for the Advancement of Science, in the Missouri Tuberculosis Association, as well as being a Fellow of the American Academy of Allergy. He was also a member of the local and regional medical groups, of the Southern Medical Association, and a Fellow of the American Medical Association. He was an assistant physician to the Barnes Hospital and a member of the staff of the Deaconess Hospital. He was an instructor in medicine in the School of Medicine, Washington University, and an assistant physician in the Medical Clinic and the Allergy Clinic of the Washington University Clinics.

He was active in Community Chest and Red Cross work and other civic and social welfare movements. His particular interest lay in the work of the Saint Louis Society for Crippled Children, of which he was serving his third term as president. He also served on the Board of the Missouri Society for Crippled Children and Adults Inc., and, at the time of his death, was a member of its cerebral palsy advisory committee.

His untimely death on June 24, 1950, by the accidental discharge of an automatic shotgun, which he was packing for a hunting and fishing trip, terminated an active and useful life and removed from our midst a vigorous, competent, and likeable physician. His death is a great loss to the field of medicine, to his friends, and to his patients.

CHARLES H. EYERMANN.

MATTHEW BRUNNER

Matthew Brunner died of leucemia at the age of 55 in Brooklyn, N. Y., on Jan. 16, 1951.

He was born in New York City on Dec. 21, 1895. Following his graduation from the New York University of Medicine in 1919, he served his interneship at the Jewish Hospital of Brooklyn until 1921, when he entered the practice of medicine and allergy in Brooklyn.

He combined a successful practice with extensive institutional and clinic work at the Jewish Hospital of Brooklyn and at the Hospital for Chronic Diseases in Brooklyn. He held the rank of Attending Physician in Allergy at both institutions. He was the author of many scientific articles in the field of allergy. He was best known for his work on sensitivity to intestinal parasites and active sensitization in human beings.

At the time of his death, he was President of the New York Allergy Society, a Fellow of the American Medical Association, of the American Academy of Allergy, and of the American College of Allergy. He was a member of the Kings County Medical Society and the New York State Medical Society.

Matthew Brunner had a unique capacity for gaining the boundless confidence of his patients and the devotion of his fellow physicians. He was calm of spirit, gentle, thoughtful of others, and possessed a keen sense of humor. To know him was to admire and to love him.

The Academy has lost a loyal friend and an esteemed colleague. We extend our deepest sympathy to his family.

MAX HARTEN,
S. SENIOR SACK,
MATTHEW WALZER.

Erratum

In the Communications Section of the January, 1951, issue of THE JOURNAL OF ALLERGY, a letter from Dr. Francis M. Rackemann stated that "Dr. Bernard N. Halpern . . . made Antergan in 1942, Neoantergan in 1948, and Phenergan in 1950." As pointed out by Dr. S. Walter Landau, this statement is not accurate. Dr. Halpern did extensive pharmacologic screening of antihistamine drugs leading to the introduction of Antergan and Phenergan, both of which had been synthetized in the laboratories of the Societe Rhone-Poulenc. Neoantergan was described in 1944 by Dr. Daniel Bovet who is now in Rome, Italy.